PRIOR AUTHORIZATION POLICY

POLICY: Allergen Immunotherapy – Grass Pollen Sublingual Products Prior Authorization Policy
- Grastek® (Timothy grass pollen allergen extract sublingual tablets – ALK-Abello)
- Oralair® (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass mixed pollens allergen extract sublingual tablets – Stallergenes/Greer)

REVIEW DATE: 09/13/2023

OVERVIEW

Grastek and Oralair are grass pollen allergen extracts indicated for **allergic rhinitis**, with or without conjunctivitis, that has been confirmed by a positive skin test or *in vitro* test for pollen-specific immunoglobulin E (IgE) antibodies for Timothy grass or cross reactive grass pollens (Grastek) or any of the five grasses contained in the product (Oralair).[1,2] These products are indicated in patients 5 through 65 years of age.

Per product labeling, Grastek must be initiated 12 weeks before the expected onset of each grass pollen season and Oralair must be initiated 4 months before the expected onset of each grass pollen season.[1,2] Both must be continued throughout the season.

Clinical Efficacy

Pivotal trials of Grastek and Oralair included patients with grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by either a positive skin prick test to Timothy grass pollen or positive *in vitro*.[1,2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Grastek and Oralair. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Grastek and Oralair is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Grass Pollen-Induced Allergic Rhinitis.** Approve for 1 year if the patient meets ALL of the following (A, B and C):
   - **A)** Patient is ≥ 5 years of age; AND
   - **B)** The timing of prescribing meets ONE of the following criteria (i or ii):
     - **i.** Grastek: Therapy is initiated 12 weeks prior to the expected onset of the grass pollen season or therapy is being dosed daily continuously for consecutive grass pollen seasons; OR
     - **ii.** Oralair: Therapy is initiated 4 months prior to the expected onset of the grass pollen season; AND
   - **C)** The diagnosis of grass pollen-induced allergic rhinitis is confirmed by meeting ONE of the following conditions (i or ii):

i. Patient has a positive skin test response to a grass pollen from the Pooideae subfamily of grasses (this includes, but is not limited to: sweet vernal, Kentucky blue grass, Timothy grass, orchard, or perennial rye grass); OR

ii. Patient has a positive *in vitro* test (i.e., a blood test) for allergen-specific immunoglobulin E antibodies for a grass in the Pooideae subfamily of grasses (see examples above).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Grastek and Oralair is not recommended in the following situations:

1. **Concurrent Use of Grastek or Oralair with Subcutaneous Allergen Immunotherapy or Sublingual Allergen Immunotherapy.** Note: This includes allergy shots as well as Odactra® [house dust mite {*Dermatophagoides farina* and *Dermatophagoides pteronyssinus*} allergen extract sublingual tablets], Ragwitek® [short ragweed pollen allergen extract sublingual tablets]). The efficacy of Grastek and Oralair has not been evaluated in patients who are receiving concomitant allergen immunotherapy.[1] Approved product labeling for both Grastek and Oralair states that concomitant dosing with other allergen immunotherapy may increase the risk of local or systemic adverse events to either subcutaneous or sublingual allergen immunotherapy. A Joint Practice Parameter specifically addressing sublingual immunotherapy (2017) highlights that no studies have evaluated the efficacy of multiple sublingual immunotherapy tablets administered together.[5] There is a need for further investigation to determine efficacy and optimal formulations for multi-allergen sublingual immunotherapy.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Grastek® sublingual tablets [prescribing information]. Swindon, Wiltshire, United Kingdom: ALK-Abello A/S; September 2022.
2. Oralair® sublingual tablets [prescribing information]. Lenoir, NC: Greer; December 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Allergen Immunotherapy – Odactra Prior Authorization Policy
- Odactra® (house dust mite [*Dermatophagoides farina* and *Dermatophagoides pteronyssinus*] allergen extract sublingual tablets – Merck)

REVIEW DATE: 09/13/2023

OVERVIEW

Odactra, a house dust mite allergen extract, is indicated as immunotherapy for **house dust mite-induced allergic rhinitis**, with or without conjunctivitis, confirmed by *in vitro* testing for immunoglobulin E (IgE) antibodies to house dust mites or skin testing to licensed house dust mite allergen extracts.[1] It is approved for use in patients 12 to 65 years of age. Odactra is not indicated for the immediate relief of allergic symptoms.

Clinical Efficacy

Pivotal trials of Odactra involved patients as young as 12 years of age with house dust mite-induced allergic rhinitis with or without conjunctivitis.[2-4] The house dust mite sensitivity was confirmed by a positive skin test response to *D. pteronyssinus* and/or *D. farina* and a specific IgE level of ≥ 0.7 kU/L against *D. pteronyssinus, D. farina* or both.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Odactra. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Odactra is recommended in those who meet the following criteria:

FDA-Approved Indication

2. **House Dust Mite-Induced Allergic Rhinitis.** Approve for 1 year if the patient meets ALL of the following (A and B):
   - **D)** Patient is ≥ 12 years of age; AND
   - **E)** The diagnosis of house dust mite-induced allergic rhinitis is confirmed by meeting ONE of the following conditions (i or ii):
     - **i.** Patient has a positive skin test response to house dust mite allergen extracts; OR
     - **ii.** Patient has a positive *in vitro* test (i.e., a blood test for allergen-specific immunoglobulin E antibodies) for house dust mite.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Odactra is not recommended in the following situations:

3. **Concurrent Use of Odactra with Subcutaneous Allergen Immunotherapy or Sublingual Allergen Immunotherapy.** Note: This includes allergy shots as well as Grastek (Timothy grass pollen allergen extract sublingual tablets), Oralair (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass mixed pollens allergen extract sublingual tablets), and Ragwitek (short ragweed pollen allergen extract sublingual tablets). The efficacy and safety of Odactra have not been evaluated in patients who are receiving concomitant allergen immunotherapy.[1] Approved product labeling for Odactra states that concomitant dosing with other allergen immunotherapy may increase the risk of local or systemic adverse events to either the subcutaneous or sublingual allergen immunotherapy.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

3. Odactra® allergen extract sublingual tablets [prescribing information]. Whitehouse Station, NJ: Merck; January 2023.
4. Nolte H, Bernstein DI, Nelson HS, et al. Efficacy of house dust mite sublingual immunotherapy tablet in North American adolescents and adults in a randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2016;138(6):1631-1638.
5. Demoly P, Emminger W, Rehm D, et al. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: results from a randomized, double-blind, placebo-controlled phase III trial. *J Allergy Clin Immunol*. 2016;137(2):444-451.
6. Nolte H, Maloney J, Nelson HS. Onset and dose-related efficacy of house dust mite sublingual immunotherapy tablets in an environmental exposure chamber. *J Allergy Clin Immunol*. 2015;135(6):1494-1501.

PRIOR AUTHORIZATION POLICY

POLICY: Allergen Immunotherapy – Palforzia Prior Authorization Policy
- Palforzia® (peanut [*Arachis hypogaea*] allergen powder-dnfp for oral administration – Aimmune)

REVIEW DATE: 03/01/2023

OVERVIEW

Palforzia, an oral immunotherapy, is indicated for the mitigation of **allergic reactions**, including anaphylaxis, that may occur with accidental exposure to peanut.[1] It is approved for use in patients with a confirmed diagnosis of peanut allergy. Initial dose escalation may be administered to patients 4 through 17 years of age; up-dosing and maintenance may be continued in patients ≥ 4 years of age. Palforzia is labeled to be used in conjunction with a peanut-avoidant diet. It is not indicated for the emergency treatment of allergic reactions, including anaphylaxis. Prior to initiation, the prescriber should verify that the patient has injectable epinephrine and has been instructed on its appropriate use.

Clinical Efficacy

The Palforzia pivotal study, PALISADE, included patients who were required to have a diagnosis of peanut allergy supported by either a serum peanut-specific immunoglobulin E (psIgE) level of ≥ 0.35 allergen-specific unit per liter (kU_A/L) or a mean wheal diameter of at least 3 mm larger than the negative control to a skin-prick test (SPT) for peanut.[2] Additionally, to be eligible for randomization, patients had to have an allergic reaction (with dose-limiting symptoms) to a prespecified dose of peanut protein during a double-blind, placebo-controlled food challenge at screening.

Guidelines

Current guidelines regarding diagnosis and management of food allergy state that parent and patient reports of food allergy must be confirmed.[3] An SPT and allergen-specific IgE testing are each recommended as a method to identify foods that provoke allergic reactions. However, each test alone cannot be considered to be diagnostic for food allergy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Palforzia. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Palforzia as well as the monitoring required for adverse events and long-term efficacy, approval requires Palforzia to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Palforzia is recommended in those who meet the following criteria:

FDA-Approved Indication

3. Peanut Allergy. Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, D, E, and F):

F) Patient meets ONE of the following (i or ii):

i. Patient is 4 to 17 years of age; OR

ii. Patient is ≥ 18 years of age AND has been previously started on therapy with Palforzia prior to becoming 18 years of age; AND

G) Per the prescriber, the patient has a of an allergic reaction to peanut that met each of the following (i, ii, and iii):

i. Patient demonstrated signs and symptoms of a significant systemic allergic reaction; AND
Note: Signs and symptoms of a significant systemic allergic reaction include hives, swelling, wheezing, hypotension, and gastrointestinal symptoms.

ii. This reaction occurred within a short period of time following a known ingestion of peanut or peanut-containing food; AND

iii. The prescriber deemed this reaction significant enough to require a prescription for an epinephrine auto-injector; AND
Note: Examples of epinephrine auto-injectors include EpiPen, EpiPen Jr., Auvi-Q, and generic epinephrine auto-injectors.

H) Patient has a positive skin prick test (SPT) response to peanut with a wheal diameter ≥ 3 mm larger than the negative control; AND

I) Patient has a positive *in vitro* test (i.e., a blood test) for peanut-specific IgE (psIgE) with a level ≥ 0.35 kU_A/L; AND

J) Per the prescriber, Palforzia will be used in conjunction with a peanut-avoidant diet; AND

K) The medication is prescribed by or in consultation with an allergist or immunologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Palforzia is not recommended in the following situations:

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

7. Palforzia® allergen powder [prescribing information]. Brisbane, CA: Aimmune; January 2020.
8. Vickery BP, Vereda A, Casale TB, et al. for the PALISADE group of clinical investigators. AR101 oral immunotherapy for peanut allergy. *N Engl J Med*. 2018;379(21):1991-2001.
9. Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel. *J Allergy Clin Immunol*. 2017;139(1):29-44.

PRIOR AUTHORIZATION POLICY

POLICY: Allergen Immunotherapy – Ragwitek Prior Authorization Policy
- Ragwitek® (short ragweed pollen allergen extract sublingual tablets – ALK-Abello)

REVIEW DATE: 09/13/2023

OVERVIEW

Ragwitek, a ragweed pollen allergen extract, is indicated as immunotherapy for the treatment of patients 5 to 65 years of age with **short ragweed pollen-induced allergic rhinitis** with or without conjunctivitis confirmed by a positive skin test or *in vitro* test for pollen-specific immunoglobulin E (IgE) antibodies for short ragweed pollen.[1] Ragwitek is not indicated for the immediate relief of allergy symptoms. Ragwitek is dosed once daily and must be initiated at least 12 weeks before the expected onset of ragweed pollen season and continued throughout the season.

Clinical Efficacy

Clinical trials of Ragwitek enrolled adults and pediatric with allergic rhinitis with or without conjunctivitis. Patients had their diagnosis confirmed by a positive skin prick test and positive *in vitro* testing for serum IgE antibodies for short ragweed.[1-4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ragwitek. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ragwitek is recommended in those who meet the following criteria:

FDA-Approved Indication

4. **Short Ragweed Pollen-Induced Allergic Rhinitis.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   - **L)** Patient is ≥ 5 years of age; AND
   - **M)** Ragwitek therapy is initiated 12 weeks prior to the expected onset of the short ragweed pollen season; AND
   - **N)** The diagnosis of short ragweed pollen-induced allergic rhinitis is confirmed by meeting ONE of the following conditions (i or ii):
     - **i.** Patient has a positive skin test response to short ragweed pollen; OR
     - **ii.** Patient has a positive *in vitro* test (i.e., a blood test) for allergen-specific immunoglobulin E antibodies for short ragweed pollen.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ragwitek is not recommended in the following situations:

6. **Concurrent Use of Ragwitek with Subcutaneous Allergen Immunotherapy or Sublingual Allergen Immunotherapy.** Note: This includes allergy shots as well as Grastek (Timothy grass pollen allergen extract sublingual tablets), Oralair (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass mixed pollens allergen extract sublingual tablets), Odactra (house dust mite {*Dermatophagoides farina* and *Dermatophagoides pteronyssinus*} allergen extract sublingual tablets). The efficacy of Ragwitek has not been evaluated in patients who are receiving concomitant allergen immunotherapy.[1] Approved product labeling for Ragwitek states that concomitant dosing with other allergen immunotherapy may increase the risk of local or systemic adverse events to either subcutaneous or sublingual allergen immunotherapy.

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

10. Ragwitek® sublingual tablets [prescribing information]. Horsholm, Denmark: ALK-Abello; September 2022.
11. Nolte H, Hebert J, Berman G, et al. Randomized controlled trial of ragweed allergy immunotherapy tablet efficacy and safety in North American adults. *Ann Allergy Asthma Immunol.* 2013:110;450-456.
12. Creticos PS, Maloney J, Bernstein DI, et al. Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults. *J Allergy Clin Immunol.* 2013:131(5);1342-1349.
13. Nolte H, Bernstein D, Nelson HS, et al. Efficacy and safety of ragweed SLIT-tablet in children with allergic rhinoconjunctivitis in a randomized, placebo-controlled trial. *J Allergy Clin Immunol Pract.* 2020;8(7):2322-2331.

PRIOR AUTHORIZATION POLICY

POLICY: Alpha$_1$-Proteinase Inhibitor Products Prior Authorization Policy

- Aralast NP® (alpha$_1$-proteinase inhibitor [human] intravenous infusion – Shire)
- Glassia® (alpha$_1$-proteinase inhibitor [human] intravenous infusion – Shire)
- Prolastin®-C and Prolastin®-C Liquid (alpha$_1$-proteinase inhibitor [human] intravenous infusion – Grifols Therapeutics)
- Zemaira® (alpha$_1$-proteinase inhibitor [human] intravenous infusion – CSL Behring)

REVIEW DATE: 12/06/2023

OVERVIEW

Alpha$_1$-proteinase inhibitor (also known as alpha$_1$-antitrypsin [AAT]), is indicated for **alpha$_1$-proteinase deficiency** as a chronic augmentation and maintenance therapy in adults with clinical evidence of emphysema.[1-5] The following products are available commercially in the US: Prolastin-C (also available as Prolastin-C Liquid), Aralast NP, Zemaira, and Glassia. The products vary in their availability and in some of their purification and viral inactivation processes.

Disease Overview

AAT deficiency is a rare, chronic, hereditary, autosomal co-dominant disorder marked by low concentrations of AAT which leads to progressive, severe emphysema that often does not manifest until the third to fourth decades of life.[1] Diagnosis of AAT deficiency begins with quantitative measurement of AAT levels in the plasma.[6] Treatment is aimed at raising serum levels of AAT above a theoretical protective threshold of 11 mcM (mcmol/L), which is equivalent to the tenth percentile of the AAT range of PI*SZ individuals; epidemiological data suggest lower probability of chronic obstructive pulmonary disease (COPD) above this level.[7] A variety of techniques have been used to measure serum AAT concentration.[8] The most commonly used technique today is nephelometry. Using this technique, a serum AAT concentration < 57 mg/dL is usually associated with AAT deficiency with lung disease. Of note, older laboratory techniques (e.g., radial immunodiffusion) measured non-purified levels of AAT, which tend to overestimate the concentration by 35% to 40%.[9] An AAT level of 80 mg/dL measured by radial immunodiffusion corresponds to a plasma AAT level of 11 mcM.

Guidelines

A European Respiratory Society (ERS) statement addresses diagnosis and treatment of pulmonary disease in AAT deficiency (2017).[6] It is noted that augmentation therapy has been shown to reduce progression of emphysema in severe AAT deficiency. There is no evidence to support efficacy of AAT augmentation therapy for current smokers of any phenotype. These guidelines support earlier American Thoracic Society (ATS)/ERS guidelines (2003) which state that intravenous augmentation therapy is recommended for individuals with established airflow obstruction from AAT deficiency.[10]

The Canadian Thoracic Society updated its guidelines (2012) regarding AAT deficiency testing and augmentation therapy.[11] The guidelines state that evidence supports the consideration of AAT augmentation therapy in non-smoking or ex-smoking patients with COPD due to emphysema and a documented AAT deficiency (level ≤ 11 mcM). Patients should also be receiving other pharmacological and non-pharmacologic therapies, including comprehensive case management and pulmonary rehabilitation.

The Medical and Scientific Advisory Committee of the Alpha-1 Foundation guidelines (2016) provide similar recommendations.[12] Intravenous AAT augmentation is strongly recommended in non-smoking or ex-smoking patients with forced expiratory volume (FEV_1) 30 to 65% of predicted due to well-documented benefit in this group. Weaker recommendations also support treatment of patients with FEV_1 below 30% of predicted or above 65% of predicted. Usual management of COPD should also be provided, with strong emphasis on facilitating tobacco cessation. Of note, AAT replacement therapy is not recommended for patients who continue to smoke.

Other Uses with Supportive Evidence

In the ATS/ERS 2003 guidelines, it is stated that AAT replacement therapy is a reasonable option for AAT deficiency-associated panniculitis.[10] Although no controlled trials provide a clear treatment recommendation, augmentation therapy with purified human $alpha_1$-proteinase inhibitor or fresh frozen plasma to restore plasma and local tissue levels of AAT appears to be rational, safe, and effective. In a review of treatment options for panniculitis in AAT deficiency, augmentation therapy with $alpha_1$-proteinase inhibitor was noted to be the most successful medical treatment.[13]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of $alpha_1$-proteinase inhibitor. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of $alpha_1$-proteinase inhibitor (e.g., Aralast NP, Glassia, Prolastin-C, Prolastin-C Liquid, Zemaira) is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. **$Alpha_1$-Antitrypsin Deficiency with Emphysema (or Chronic Obstructive Pulmonary Disease).** Approve for 1 year if the patient meets the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has a baseline (pretreatment) $alpha_1$-antitrypsin serum concentration of 11 mcM (11 mcmol/L) [< 80 mg/dL if measured by radial immunodiffusion or < 57 mg/dL if measured by nephelometry]; AND
   - **C)** According to the prescriber, the patient is a current non-smoker.

Other Uses with Supportive Evidence

2. **$Alpha_1$-Antitrypsin Deficiency-Associated Panniculitis.** Approve for 1 year if the patient is ≥ 18 years of age.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of alpha1-proteinase inhibitor is not recommended in the following situations:

1. **Alpha$_1$-Antitrypsin Deficiency without Lung Disease, even if Deficiency-Induced Hepatic Disease is Present**. The ATS/ERS standards for the diagnosis and management of individuals with AAT deficiency (2003) state that the pathophysiology of liver disease in AAT deficiency is different from that of lung disease, and the use of alpha$_1$-proteinase inhibitor is not discussed for these patients.[10] There is an absence of information that suggests alpha$_1$-proteinase inhibitor is useful in patients with AAT deficiency-related liver disease.

2. **Bronchiectasis (without alpha$_1$-antitrypsin deficiency).** Studies have not demonstrated alpha$_1$ proteinase inhibitor to be effective for this condition. The ATS/ERS standards for the diagnosis and management of individuals with AAT deficiency (2003) state that despite the well-recognized association between AAT deficiency and the early development of emphysema, only a limited number of studies have assessed the association between AAT deficiency and bronchiectasis.[10] Studies suggest that bronchiectasis is more a result of emphysematous changes in the parenchyma than of AAT deficiency.

3. **Chronic Obstructive Pulmonary Disease (COPD) without Alpha$_1$-Antitrypsin Deficiency.** The Global Initiative for Chronic Obstructive Lung Disease guidelines for the diagnosis, management, and prevention of COPD (updated 2023) state that never or ex-smokers with an FEV_1 of 35 to 60% of predicted may be most suitable for AAT deficiency augmentation therapy; newer evidence suggests that individuals with higher FEV_1 values may also be candidates.[14] However, this therapy is not recommended for COPD that is unrelated to AAT deficiency.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Aralast NP® intravenous infusion [prescribing information]. Lexington, MA: Shire; December 2022.
2. Zemaira® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; September 2022.
3. Prolastin®-C intravenous infusion [prescribing information]. Research Triangle Park, NC: Grifols Therapeutics; January 2022.
4. Prolastin®-C Liquid intravenous infusion [prescribing information]. Research Triangle Park, NC: Grifols Therapeutics; May 2020.
5. Glassia® intravenous infusion [prescribing information]. Lexington, MA: Shire; September 2022.
6. Miravitlles M, Dirksen A, Ferrarotti I, et al. European Respiratory Society statement: diagnosis and treatment of pulmonary disease in alpha1-antitrypsin deficiency. *Eur Respir J.* 2017;50(5).
7. Brantly ML, Lascano JE, Shahmohammadi A. Intravenous alpha-1 antitrypsin therapy for alpha-1 antitrypsin deficiency: the current state of the evidence. *Chronc Obstr Pulm Dis.* 2018;6(1):100-114.
8. Stoller JK, Lacbawan FL, Aboussouan LS. Alpha-1 Antitrypsin Deficiency. 2006 Oct 27 [Updated 2023 June 01]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1519. Accessed on November 28, 2023.
9. Miravitlles M, Herr C, Ferrarotti I, et al. Laboratory testing of individuals with severe alpha1-antitrypsin deficiency in three European centres. *Eur Respir J.* 2010 May;35(5):960-968.
10. American Thoracic Society and the European Respiratory Society. Standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med.* 2003;168:818-900.
11. Marciniuk DD, Hernandez P, Balter M, et al. Alpha-1 antitrypsin deficiency targeted testing and augmentation therapy: A Canadian Thoracic Society clinical practice guideline. *Can Respir J.* 2012;19:109-116.
12. Sandhaus RA, Turino G, Brantly ML, et al. The diagnosis and management of alpha-1 antitrypsin deficiency in the adult. *Chronic Obstr Pulm Dis.* 2016;3(3):668-682.
13. Sabbagh DK, Barmayehvar B, Nguyen T, Edgar RG, Turner AM. Managing panniculitis in alpha-1 antitrypsin deficiency: systematic review of evidence behind treatment. *World J Dermatol.* 2018;7(1):1-8.

14. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2023. Available at: https://goldcopd.org/2024-gold-report/. Accessed on November 28, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Amifampridine Products Prior Authorization Policy
- Firdapse® (amifampridine tablets – Catalyst)
- Ruzurgi® (amifampridine tablets – Jacobus [approval withdrawn])

REVIEW DATE: 07/12/2023

OVERVIEW

Amifampridine, a broad spectrum potassium channel blocker, is indicated for the **treatment of Lambert-Eaton myasthenic syndrome** (LEMS).[1,2]

- Firdapse is indicated in **adults and pediatric patients ≥ 6 years of age**.[1]
- Ruzurgi was indicated in **patients 6 years to < 17 years of age** (prior to withdrawal of FDA approval).[2]

As of February 01, 2022, the FDA has withdrawn approval for Ruzurgi. Firdapse was approved by the FDA on November 28, 2018, for the treatment of LEMS in adults, with 7 years of orphan-drug exclusivity (ODE). On May 6, 2019, Ruzurgi was approved by the FDA for the treatment of LEMS in patients 6 to < 17 years of age. On June 12, 2019, Catalyst (manufacturer of Firdapse) brought suit against the FDA, challenging the FDA's approval of Ruzurgi stating that it violated the ODE for Firdapse. In 2022, the Court of Appeals for the Eleventh Circuit sided with Catalyst; therefore, the FDA had to withdraw approval for Ruzurgi. Due to the 7-year ODE for Firdapse, Ruzurgi may not be approved for marketing until ODE has expired on November 28, 2025.

Disease Overview

LEMS is a rare autoimmune disorder affecting the connection between nerves and muscles and causing proximal muscle weakness, autonomic dysfunction, and areflexia.[3,4] The characteristic weakness is thought to be caused by antibodies generated against the P/Q-type voltage-gated calcium channels present on presynaptic nerve terminals and by diminished release of acetylcholine.[4] The diagnosis of LEMS is confirmed by electrodiagnostic studies, including repetitive nerve stimulation, or anti-P/Q-type voltage-gated calcium channels antibody testing.

Clinical Efficacy

Firdapse was approved based on two pivotal trials.[1,5] One pivotal trial enrolled both amifampridine-naïve and treatment-experienced patients; patients were initially entered into an open-label run-in phase lasting 90 days.[5] During the open-label run-in phase, Firdapse was titrated for each individual patient to a dose that produced optimal neuromuscular benefit and tolerability in the opinion of the investigator. In order to continue in the study, treatment-naïve patients were required to have an improvement of at least three points in the quantitative myasthenia gravis score from the initial evaluation. For its pediatric indication, use is supported by evidence from studies of Firdapse in adults with LEMS, pharmacokinetic data in adults, pharmacokinetic modeling and simulation to identify the dosing regimen in pediatric patients, and safety data from pediatric patients ≥ 6 years of age.

Safety

Firdapse and Ruzurgi are contraindicated in patients with a history of seizures.[1,2] There is also a Warning/Precaution in the prescribing information for these medications because seizures have been observed in patients with and without a history of seizures taking amifampridine at the recommended doses.

Many of these patients were taking medications or had comorbidities that may have lowered their seizure threshold. Seizures may be dose-dependent.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of amifampridine. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with amifampridine as well as the monitoring required for adverse events and long-term efficacy, initial approval requires amifampridine to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of amifampridine is recommended in those who meet the following criteria:

FDA-Approved Indications

5. **Lambert-Eaton Myasthenic Syndrome (LEMS).** Approve amifampridine for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial therapy. Approve amifampridine for 3 months if the patient meets the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 6 years of age; AND
     - **ii.** Patient has confirmed LEMS based on at least one of the following, according to the prescriber:
       - **a)** Electrodiagnostic study (e.g., repetitive nerve stimulation); OR
       - **b)** Anti-P/Q-type voltage-gated calcium channels antibody testing; AND
     - **iii.** Patient does not have a of seizures; AND
     - **iv.** Amifampridine is being prescribed by or in consultation with a neurologist or a neuromuscular specialist; OR
   - **B)** Patient is Currently Receiving amifampridine. Approve amifampridine for 1 year if the patient is continuing to derive benefit from amifampridine, according to the prescriber.
     Note: Examples of continued benefit include improved muscle strength and improvements in mobility.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of amifampridine is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Firdapse® tablets [prescribing information]. Coral Gables, FL: Catalyst; May 2023.
2. Ruzurgi® tablets [prescribing information]. Princeton, NJ: Jacobus; April 2020.
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PRIOR AUTHORIZATION POLICY

POLICY: Amyloidosis – Amvuttra Prior Authorization Policy
- Amvuttra™ (vutrisiran subcutaneous injection – Alnyam)

REVIEW DATE: 06/28/2023; selected revision 01/03/2024

OVERVIEW

Amvuttra, a transthyretin (TTR)-directed small interfering RNA, is indicated for the treatment of **polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR)** in adults.[1] Amvuttra has not been studied in patients with prior liver transplantation.[6] hATTR is a progressive disease caused by mutations in the TTR gene leading to multisystem organ dysfunction.[2] Common neurologic manifestations include sensiomotor polyneuropathy, autonomic neuropathy, small-fiber polyneuropathy, and carpal tunnel syndrome.

Guidelines

There are no guidelines that include recommendations for Amvuttra. A scientific statement from the American Heart Association (AHA) on the treatment of the cardiomyopathy of hATTR amyloidosis (July 2020) includes recommendations related to polyneuropathy.[3] Canadian guidelines for the treatment of patients with polyneuropathy (February 2021) and recommendations from the European Society of Cardiology (ESC) [2021] include treatment recommendations for hATTR polyneuropathy as well.[2,4] In general, Onpattro® (patisiran intravenous infusion) and Tegsedi® (inotersen subcutaneous injection) are recommended for patients with hATTR polyneuropathy.

For patients with hATTR amyloidosis with polyneuropathy, the AHA recommends treatment with Onpattro or Tegsedi.[3] For patients with hATTR with polyneuropathy and cardiomyopathy, Onpattro, Tegsedi, or Vyndamax® (tafamidis meglumine capsules)/Vyndaqel™ (tafamidis capsules) are recommended. Use of combination therapy is discussed; however, it is noted that there is little data to support combination therapy.

The Canadian guidelines recommend Onpattro and Tegsedi as first-line treatment to stop the progression of neuropathy and improve polyneuropathy in early and late stage hATTR amyloidosis with polyneuropathy.[2]

The ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure note that TTR stabilization and reduction are the recommended basis of treatment for cardiomyopathy of hATTR.[4] Onpattro and Tegsedi may be considered for patients with hATTR polyneuropathy and cardiomyopathy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Amvuttra. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Amvuttra as well as the monitoring required for adverse events and long-term efficacy, approval requires Amvuttra to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Amvuttra is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis (hATTR).** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥18 years of age; AND
   - **B)** Patient has a transthyretin mutation as confirmed by genetic testing; AND
   - **C)** Patient has symptomatic polyneuropathy; AND
     Note: Examples of symptomatic polyneuropathy include reduced motor strength/coordination, and impaired sensation (e.g., pain, temperature, vibration, touch). Examples of assessments for symptomatic disease include history and clinical exam, electromyography, or nerve conduction velocity testing.
   - **D)** Patient does not have a of liver transplantation; AND
   - **E)** The medication is prescribed by or in consultation with a neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Amvuttra is not recommended in the following situations:

2. **Concomitant Use With Onpattro (patisiran intravenous infusion), Tegsedi (inotersen subcutaneous injection), Wainua (eplontersen subcutaneous injection), or a Tafamidis Product.**
   Note: Examples of tafamidis products are Vyndaqel and Vyndamax.
   There are insufficient data supporting the safety and efficacy of concurrent use of these agents for hereditary transthyretin-mediated amyloidosis with polyneuropathy. The Vyndaqel/Vyndamax pivotal trial, which took place prior to when Onpattro and Tegsedi were under investigation for amyloidosis, did not include patients who were taking investigational drugs. The pivotal trials for Amvuttra, Onpattro, Tegsedi, and Wainua did not allow concurrent use of tetramer stabilizers (e.g., tafamidis, diflunisal). The pivotal trials for Amvuttra and Wainua did not allow concurrent use of Onpattro or Tegsedi (Amvuttra was not approved when Wainua was under investigation). A Phase II open-label extension study (n = 27) included 13 patients who were treated concomitantly with Onpattro and tafamidis.[5] Following 24 months of treatment, there was no significant difference in the median serum transthyretin percent change from baseline with concomitant Onpattro and tafamidis (-80%) vs. Onpattro monotherapy (-88%). A scientific statement from the AHA notes that there is little data to support combination therapy for these products.[3]

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Amyloidosis – Onpattro Prior Authorization Policy
- Onpattro® (patisiran intravenous infusion – Alnylam)

REVIEW DATE: 11/29/2023; selected revision 01/03/2024

OVERVIEW

Onpattro, a lipid nanoparticle formulated RNA interference therapeutic, is indicated for treatment of adults with **polyneuropathy of hereditary amyloid transthyretin amyloidosis (hATTR)**.[1] hATTR is a progressive disease caused by mutations in the transthyretin (TTR) gene leading to multisystem organ dysfunction.[2] Common neurologic manifestations include sensiomotor polyneuropathy, autonomic neuropathy, small-fiber polyneuropathy, and carpal tunnel syndrome.

Clinical Efficacy

The pivotal trial for Onpattro did not include patients with liver transplantation, which has historically been a treatment modality for hATTR.[1,6] A Phase IIIb, open-label trial evaluated the efficacy of Onpattro in adults with hATTR polyneuropathy progression post liver transplant (n = 23).[6] Patients received Onpattro at the FDA-approved dose for 12 months. The average of Month 6 and Month 12 serum TTR reduction was 91%. In addition, improvements in neuropathy, quality of life, autonomic symptoms from baseline to Month 12, and stabilized disability and nutritional status was noted. The prescribing information for Onpattro notes that age, race (non-Caucasian vs. Caucasian), sex, and prior liver transplantation had no impact on the steady state pharmacokinetics of Onpattro or TTR reduction.[1]

APOLLO-B was a Phase III, double-blind, trial that randomized patients with hATTR cardiac amyloidosis to receive Onpattro or placebo for 12 months (n = 360).[7] The primary endpoint was a change from baseline in the distance walked on 6-minute walk test. The first secondary endpoint was the change from baseline to Month 12 in the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score. A composite of death from any cause, cardiovascular events, and change from baseline in the 6-minute walk test distance over 12 months, was a secondary endpoint. A third secondary endpoint assessed the composite of death from any cause, hospitalization for any cause, and urgent heart failure visits. At Month 12, the magnitude of decline in 6-minute walk distance was significantly lower in the Onpattro group (-8.15 meters) vs. placebo (-21.35 meters) [median difference 14.69 meters; 95% confidence interval [CI]: 0.69, 28.69; P = 0.02). The KCCQ-OS score was slightly improved with Onpattro (+0.3 points), but reduced with placebo (-3.4 points), leading to a statistically significant between group difference (3.7 points; 95% CI: 0.2, 7.2; P = 0.04). The secondary composite endpoints were not significant between groups. Based on these findings, the FDA cited insufficient evidence of clinical meaningfulness for the treatment of cardiomyopathy of hATTR and issued a complete response letter to the manufacturer of Onpattro for the treatment of cardiomyopathy of hATTR.[8]

Guidelines

A scientific statement from the American Heart Association (AHA) on the treatment of cardiomyopathy of hATTR amyloidosis (July 2020) includes recommendations related to polyneuropathy.[3] Canadian guidelines for the treatment of patients with polyneuropathy (February 2021) and recommendations from the European Society of Cardiology (ESC) [2021] include treatment recommendations for hATTR polyneuropathy as well.[2,4] The American College of Cardiology (ACC) expert consensus decision pathway on comprehensive multidisciplinary care for patients with cardiac amyloidosis (2023) mention Onpattro for polyneuropathy of hATTR; but, it is noted that the product is not indicated for cardiomyopathy of hATTR

amyloidosis (APOLLO-B trial results are acknowledged).[9] In general, Onpattro and Tegsedi® (inotersen subcutaneous injection) are recommended for patients with hATTR polyneuropathy.

For patients with hATTR amyloidosis with polyneuropathy, the AHA recommends treatment with Onpattro or Tegsedi.[3] For patients with hATTR with polyneuropathy and cardiomyopathy, Onpattro, Tegsedi, or Vyndamax™ (tafamidis capsules)/Vyndaqel® (tafamidis meglumine capsules) are recommended. Use of combination therapy is discussed; however, it is noted that there is little data to support combination therapy.

The Canadian guidelines recommend Onpattro and Tegsedi as first-line treatment to stop the progression of neuropathy and improve polyneuropathy in early and late stage hATTR amyloidosis with polyneuropathy.[2]

The ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure note that TTR stabilization and reduction are the recommended basis of treatment for cardiomyopathy of ATTR.[4] Onpattro and Tegsedi may be considered for patients with hATTR polyneuropathy and cardiomyopathy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Onpattro. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Onpattro as well as the monitoring required for adverse events and long-term efficacy, approval requires Onpattro to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Onpattro is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis (hATTR).** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   - **F)** Patient is ≥18 years of age; AND
   - **G)** Patient has a transthyretin mutation as confirmed by genetic testing; AND
   - **H)** Patient has symptomatic polyneuropathy; AND
     Note: Examples of symptomatic polyneuropathy include reduced motor strength/coordination, and impaired sensation (e.g., pain, temperature, vibration, touch). Examples of assessments for symptomatic disease include and clinical exam, electromyography, or nerve conduction velocity testing.
   - **I)** The medication is prescribed by or in consultation with a neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

1. Coverage of Onpattro is not recommended in the following situations:

8. Concomitant Use With Amvuttra (vutrisiran subcutaneous injection), Tegsedi (inotersen subcutaneous injection), Wainua (eplontersen subcutaneous injection), or a Tafamidis Product.
Note: Examples of tafamidis products are Vyndaqel and Vyndamax.
There are insufficient data supporting the safety and efficacy of concurrent use of these agents for hATTR with polyneuropathy. The Vyndaqel/Vyndamax pivotal trial, which took place prior to when Onpattro and Tegsedi were under investigation for amyloidosis, did not include patients who were taking investigational drugs. The pivotal trials for Amvuttra, Onpattro Tegsedi, and Wainua did not allow concurrent use of tetramer stabilizers (e.g., tafamidis, diflunisal). The pivotal trials for Amvuttra and Wainua did not allow concurrent use of Onpattro or Tegsedi (Amvuttra was not approved when Wainua was under investigation). A Phase II open-label extension study (n = 27) included 13 patients who were treated concomitantly with Onpattro and tafamidis.[5] Following 24 months of treatment, there was no significant difference in the median serum TTR percent change from baseline with concomitant Onpattro and tafamidis (-80%) vs. Onpattro monotherapy (-88%). A scientific statement from the American Heart Association notes that there is little data to support combination therapy for these products.[3]

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Amyloidosis – Tafamidis Products Prior Authorization Policy
- Vyndaqel (tafamidis meglumine capsules – Pfizer)
- Vyndamax (tafamidis capsules – Pfizer)

REVIEW DATE: 11/29/2023; selected revision 01/03/2024

OVERVIEW

Vyndaqel and Vyndamax are selective stabilizers of transthyretin (TTR) indicated for the treatment of the **cardiomyopathy of wild-type or hereditary TTR-mediated amyloidosis** (ATTR-CM) to reduce cardiovascular mortality and cardiovascular-related hospitalization in adults.[1] Studies excluded patients with New York Heart Association class IV disease.[2]

Disease Overview

In ATTR-CM, there is misfolding of the TTR protein resulting in accumulation of amyloid in the heart causing thickening of both ventricles.[2-8] ATTR-CM may be suspected following cardiac imaging (e.g., echocardiogram, cardiac magnetic imaging). Subsequent testing (e.g., scintigraphy or biopsy) confirms the diagnosis of ATTR-CM. Endomyocardial biopsy confirms the diagnosis of ATTR-CM.[8] Biopsy can confirm if ATTR-CM is due to a hereditary mutant variant of TTR vs. an acquired wild-type variant. In patients with confirmed cardiac amyloidosis, TTR gene sequencing aids in treatment decisions and is necessary for genetic counseling in relatives of patients with a TTR variant.[7] Although many mutations have been identified, mutation of V122I is the most common in the US.[2-6] This mutation is present in 3% to 4% of African Americans and is associated with amyloid cardiomyopathy. Vyndaqel and Vyndamax bind to TTR at the thyroxine binding sites and stabilize the tetramer. This slows dissociation into monomers, which is the rate-limiting step in the amyloidogenic process.[1]

Guidelines

The American Heart Association (AHA) scientific statement for the evolving diagnosis and management of cardiac amyloidosis (2020) recognizes tafamidis as a treatment for ATTR-CM.[7] They note that the benefit of tafamidis has not been observed in patients with NYHA class IV symptoms. Additionally, although combination use of tafamidis with Onpattro® (patisiran lipid complex intravenous infusion) or Tegsedi® (inotersen subcutaneous injection) is appealing to target both TTR silencing and stabilization for the remaining synthesized protein, this approach lacks data and may be cost-prohibitive. Tafamidis should generally be considered the agent of choice in ATTR-CM in patients with reasonable expected survival according to a position statement of the European Society of Cardiology (ESC) working group on myocardial and pericardial disease (2021).[8] The working group notes that tafamidis is the only drug that has shown efficacy in a randomized trial in patients with ATTR-CM and should be considered in patients with reasonable expected survival. The American College of Cardiology (ACC) expert consensus decision pathway on comprehensive multidisciplinary care for patients with cardiac amyloidosis (2023) make similar comments and recommendations to the AHA and ESC regarding tafamidis.[10]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of tafamidis products (Vyndaqel and Vyndamax). Because of the specialized skills required for evaluation and diagnosis of patients treated with tafamidis products (Vyndaqel and Vyndamax) as well as the monitoring required for adverse events and

long-term efficacy, initial approval requires the agent to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of tafamidis products (Vyndaqel and Vyndamax) is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Cardiomyopathy of Wild-Type or Hereditary Transthyretin Amyloidosis.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** The diagnosis was confirmed by ONE of the following (i, ii, or iii):
     - **i.** A technetium pyrophosphate scan (i.e., nuclear scintigraphy); OR
     - **ii.** Amyloid deposits are identified on cardiac biopsy; OR
     - **iii.** Patient had genetic testing which, according to the prescriber, identified a transthyretin (TTR) mutation; AND
       Note: Examples of TTR mutations include Val122Ile mutation and Thr60Ala mutation. If the patient has wild-type amyloidosis, this is **not** a TTR mutation.
   - **C)** Diagnostic cardiac imaging has demonstrated cardiac involvement; AND
     Note: Examples of cardiac imaging include echocardiogram and cardiac magnetic imaging. Examples of cardiac involvement on imaging include increased thickness of the ventricular wall or interventricular septum.
   - **D)** Patient has heart failure, but does **not** have New York Heart Association class IV disease; AND
   - **E)** The medication is prescribed by or in consultation with a cardiologist or a physician who specializes in the treatment of amyloidosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of tafamidis products (Vyndaqel and Vyndamax) is not recommended in the following situations:

10. **Concomitant Use With Amvuttra (vutrisiran subcutaneous injection), Onpattro (patisiran lipid complex intravenous infusion), Tegsedi (inotersen subcutaneous injection), or Wainua (eplontersen subcutaneous injection).** There are no data supporting the safety and efficacy of concurrent use with Vyndaqel/Vyndamax. The Vyndaqel/Vyndamax pivotal trial, which took place prior when Onpattro and Tegsedi were under investigation for amyloidosis, did not include patients who were taking investigational drugs. The pivotal trials for Amvuttra, Onpattro, Tegsedi, and Wainua did not allow concurrent use of tetramer stabilizers (e.g., tafamidis, diflunisal). The pivotal trials for Amvuttra and Wainua did not allow concurrent use of Onpattro or Tegsedi (Amvuttra was not approved when Eplontersen was under investigation). A Phase II open-label extension study, included 13 patients who were treated with concomitantly with Onpattro and tafamidis.[7] Following 24 months of treatment, there was not significant difference in the median serum TTR percent change from baseline with concomitant Onpattro and tafamidis (-80%) vs. Onpattro monotherapy (-88%). A scientific statement from the American Heart Association notes that there is little data to support combination therapy for these products.[8]

11. **Concurrent Use of Vyndaqel and Vyndamax.** There are no data available to support concomitant use.

12. **Polyneuropathy of Hereditary Transthyretin–Mediated Amyloidosis (hATTR).** Neither Vyndaqel nor Vyndamax are indicated for treatment of symptoms of polyneuropathy associated with hATTR.
    Note: For patients with hATTR and cardiomyopathy or mixed phenotype (concurrent cardiomyopathy and polyneuropathy), refer to FDA-Approved Indication, above.

13. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Amyloidosis – Tegsedi Prior Authorization Policy

- Tegsedi® (inotersen subcutaneous injection – Ionis/Akcea Therapeutics)

REVIEW DATE: 11/29/2023; selected revision 01/03/2024

OVERVIEW

Tegsedi, an antisense oligonucleotide, is indicated for treatment of adults with **polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR)**.[1] Tegsedi has not been studied in patients with a history of liver transplantation. hATTR is a progressive disease caused by mutations in the transthyretin (TTR) gene leading to multisystem organ dysfunction.[2] Common neurologic manifestations include sensiomotor polyneuropathy, autonomic neuropathy, small-fiber polyneuropathy, and carpal tunnel syndrome.

Guidelines

A scientific statement from the American Heart Association (AHA) on the treatment of cardiomyopathy of hATTR (July 2020) includes recommendations related to polyneuropathy.[3] Canadian guidelines for the treatment of patients with polyneuropathy (February 2021) and recommendations from the European Society of Cardiology (ESC) [2021] include treatment recommendations for hATTR polyneuropathy as well.[2,4] The American College of Cardiology (ACC) expert consensus decision pathway on comprehensive multidisciplinary care for patients with cardiac amyloidosis (2023) mention Tegsedi for polyneuropathy of hATTR.[5] In general, Onpattro and Tegsedi are recommended for patients with hATTR polyneuropathy.

For patients with hATTR with polyneuropathy, the AHA recommends treatment with Onpattro or Tegsedi.[3] For patients with hATTR with polyneuropathy and cardiomyopathy, Onpattro, Tegsedi, or Vyndamax/Vyndaqel are recommended. Use of combination therapy is discussed; however, it is noted that there is little data to support combination therapy.

The Canadian guidelines recommend Onpattro and Tegsedi as first-line treatment to stop the progression of neuropathy and improve polyneuropathy in early and late stage hATTR with polyneuropathy.[2]

The ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure note that TTR stabilization and reduction are the recommended basis of treatment for cardiomyopathy of hATTR.[4] Onpattro and Tegsedi may be considered for patients with hATTR polyneuropathy and cardiomyopathy.

Safety

Tegsedi has a Boxed Warning regarding sudden and unpredictable thrombocytopenia which may be life-threatening.[1] It is contraindicated in patients with a platelet count less than 100 x 10^9/L. Based on monitoring, Tegsedi may need to be interrupted or discontinued. Following discontinuation, continue to monitor platelet counts for 8 weeks (or longer if platelet count is less than 100 x 10^9/L). Tegsedi also has a Boxed Warning regarding glomerulonephritis, which may require immunosuppressive treatment and may lead to dialysis-dependent renal failure. Due to the risks and frequent monitoring for both serious bleeding caused by severe thrombocytopenia and because of glomerulonephritis, Tegsedi is only available through a restricted distribution program under the Tegsedi REMS (Risk Evaluation and Mitigation Strategy).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tegsedi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tegsedi as well as the monitoring required for adverse events and long-term efficacy, approval requires Tegsedi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tegsedi is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Polyneuropathy of Hereditary Transthyretin–Mediated Amyloidosis (hATTR).** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has a transthyretin mutation as confirmed by genetic testing; AND
   - **C)** Patient has symptomatic polyneuropathy; AND
     Note: Examples of polyneuropathy include reduced motor strength/coordination, and impaired sensation (e.g., pain, temperature, vibration, touch). Examples of assessments for symptomatic disease include history and clinical exam, electromyography, or nerve conduction velocity testing.
   - **D)** Patient does not have a of liver transplantation; AND
   - **E)** The medication is prescribed by or in consultation with a neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis.

2.

3.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tegsedi is not recommended in the following situations:

14. **Concomitant Use With Amvuttra (vutrisiran subcutaneous injection), Onpattro (patisiran lipid complex intravenous infusion), Wainua (eplontersen subcutaneous injection), or a Tafamidis Product.**
    Note: Examples of tafamidis products are Vyndaqel and Vyndamax.
    There are insufficient data supporting the safety and efficacy of concurrent use of these agents for hATTR with polyneuropathy. The Vyndaqel/Vyndamax pivotal trial, which took place prior to when Onpattro and Tegsedi were under investigation for amyloidosis, did not include patients who were taking investigational drugs. The pivotal trials for Amvuttra, Onpattro, Tegsedi, and Wainua did not allow concurrent use of tetramer stabilizers (e.g., tafamidis, diflunisal). The pivotal trials for Amvuttra and Wainua did not allow concurrent use of Onpattro or Tegsedi (Amvuttra was not approved when Wainua was under investigation). A scientific statement from the American Heart Association notes that there is little data to support combination therapy for these products.[3]

15. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Tegsedi® injection [prescribing information]. Carlsbad, CA: Ionis/Akcea Therapeutics; July 2020.
2. Alcantara M, Mezi MM, Baker SK, et al. Canadian guidelines for hereditary transthyretin amyloidosis polyneuropathy management. *Can J Nero Sci*. 2022;49:7-18.
10. Kittleson MM, Maurer MS, Ambardekar AV, et al; on behalf of the American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology. AHA scientific statement: cardiac amyloidosis: evolving diagnosis and management. *Circulation*. 2020;142:e7-e22.
11. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599-3726.
12. Kittleson M, Ruberg FL, Ambardekar AV, et al. A report of the American College of Cardiology Solution Set Oversight Committee. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis. *JACC*. 2023;81(11):1076-1126.

PRIOR AUTHORIZATION POLICY

POLICY: Amyloidosis – Wainua Prior Authorization Policy
- Wainua™ (eplontersen subcutaneous injection – AstraZeneca)

REVIEW DATE: 01/03/2024

OVERVIEW

Wainua, a transthyretin (TTR)-directed antisense oligonucleotide, is indicated for the treatment of the **polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR)** in adults.[1] Wainua has not been studied in patients with prior liver transplantation. hATTR is a progressive disease caused by mutations in the TTR gene leading to multisystem organ dysfunction.[2] Common neurologic manifestations include sensiomotor polyneuropathy, autonomic neuropathy, small-fiber polyneuropathy, and carpal tunnel syndrome.

Guidelines

There are no guidelines that include recommendations for Wainua. A scientific statement from the American Heart Association (AHA) on the treatment of the cardiomyopathy of hATTR amyloidosis (July 2020) includes recommendations related to polyneuropathy.[3] Canadian guidelines for the treatment of patients with polyneuropathy (February 2021) and recommendations from the European Society of Cardiology (ESC) [2021] include treatment recommendations for hATTR polyneuropathy as well.[2,4] In general, Onpattro® (patisiran intravenous infusion) and Tegsedi® (inotersen subcutaneous injection) are recommended for patients with hATTR polyneuropathy.

For patients with hATTR amyloidosis with polyneuropathy, the AHA recommends treatment with Onpattro or Tegsedi.[3] For patients with hATTR with polyneuropathy and cardiomyopathy, Onpattro, Tegsedi, or Vyndamax® (tafamidis meglumine capsules)/Vyndaqel™ (tafamidis capsules) are recommended. Use of combination therapy is discussed; however, it is noted that there is little data to support combination therapy.

The Canadian guidelines recommend Onpattro and Tegsedi as first-line treatment to stop the progression of neuropathy and improve polyneuropathy in early and late stage hATTR amyloidosis with polyneuropathy.[2]

The ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure note that TTR stabilization and reduction are the recommended basis of treatment for cardiomyopathy of hATTR.[4] Onpattro and Tegsedi may be considered for patients with hATTR polyneuropathy and cardiomyopathy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Wainua. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Wainua as well as the monitoring required for adverse events and long-term efficacy, approval requires Wainua to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Wainua is recommended in those who meet the following criteria:

FDA-Approved Indication

2. **Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis (hATTR).** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   J) Patient is ≥18 years of age; AND
   K) Patient has a transthyretin mutation as confirmed by genetic testing; AND
   L) Patient has symptomatic polyneuropathy; AND
   Note: Examples of symptomatic polyneuropathy include reduced motor strength/coordination, and impaired sensation (e.g., pain, temperature, vibration, touch). Examples of assessments for symptomatic disease include history and clinical exam, electromyography, or nerve conduction velocity testing.
   M) Patient does not have a of liver transplantation; AND
   N) The medication is prescribed by or in consultation with a neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Wainua is not recommended in the following situations:

4. **Concomitant Use With Amvuttra (vutrisiran subcutaneous injection), Onpattro (patisiran intravenous infusion), Tegsedi (inotersen subcutaneous injection), or a Tafamidis Product.**
   Note: Examples of tafamidis products are Vyndaqel and Vyndamax.
   There are insufficient data supporting the safety and efficacy of concurrent use of these agents for hereditary transthyretin-mediated amyloidosis with polyneuropathy. The Vyndaqel/Vyndamax pivotal trial, which took place prior to when Onpattro and Tegsedi were under investigation for amyloidosis, did not include patients who were taking investigational drugs. The pivotal trials for Amvuttra, Onpattro, Tegsedi, and Wainua did not allow concurrent use of tetramer stabilizers (e.g., tafamidis, diflunisal). A Phase II open-label extension study (n = 27) included 13 patients who were treated concomitantly with Onpattro and tafamidis.[5] Following 24 months of treatment, there was no significant difference in the median serum transthyretin percent change from baseline with concomitant Onpattro and tafamidis (-80%) vs. Onpattro monotherapy (-88%). A scientific statement from the AHA notes that there is little data to support combination therapy for these products.[3]

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

13. Wainua™ subcutaneous injection [prescribing information]. Wilmington, DE: AstraZeneca; December 2023.
14. Alcantara M, Mezi MM, Baker SK, et al. Canadian guidelines for hereditary transthyretin amyloidosis polyneuropathy management. *Can J Nero Sci*. 2022;49:7-18.
15. Kittleson MM, Maurer MS, Ambardekar AV, et al; on behalf of the American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology. AHA scientific statement: cardiac amyloidosis: evolving diagnosis and management. *Circulation*. 2020;142:e7-e22.
16. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599-3726.
17. Lin H, Merkel M, Hale C, Marantz JL. Experience of patisiran with transthyretin stabilizers in patients with hereditary transthyretin-mediated amyloidosis. *Neurodegener Dis Manag*. 2020;10(5):289-300.
18. Coelho T, Ando Y, Benson MD, et al. Design and rationale of the global Phase 3 NEURO-TTransform Study of antisense oligonucleotide AKCEA-TTR-L_{rx} (ION-682884-CS3) in hereditary transthyretin-mediated amyloid polyneuropathy. *Neurol Ther*. 2021;10:375-389.

PRIOR AUTHORIZATION POLICY

POLICY: Antibiotics (Inhaled) – Arikayce Prior Authorization Policy
- Arikayce® (amikacin liposome suspension for oral inhalation – Insmed)

REVIEW DATE: 10/25/2023

OVERVIEW

Arikayce is indicated for the treatment of ***Mycobacterium avium* complex (MAC) lung disease**, in adults who have limited or no alternative treatment options, as part of a combination antibacterial regimen in patients who do not achieve negative sputum cultures after at least 6 consecutive months of a background multidrug regimen (MDR) therapy.[1] As only limited clinical safety and efficacy data are available, reserve Arikayce for adults with limited or no other treatment options.

This indication was approved under accelerated approval based on achieving sputum culture conversion (defined as three consecutive negative monthly sputum cultures) by Month 6.[1]

Limitation of Use: Arikayce has only been studied in patients with refractory MAC lung disease defined as not achieving culture negativity after at least 6 months of background MDR treatment.[1] Arikayce is not recommended in patients with non-refractory MAC lung disease.

Efficacy

The efficacy of Arikayce was established in one open-label, randomized (2:1), multi-center trial in patients with refractory MAC lung disease as confirmed by at least 2 sputum culture results (n = 336).[7] Patients were considered to have refractory MAC lung disease if they did not achieve negative sputum cultures after a minimum duration of 6 consecutive months of background regimen therapy that was either ongoing or stopped ≤ 12 months before the screening visit. The surrogate efficacy endpoint was based on achieving culture conversion (3 consecutive monthly negative sputum cultures) by Month 6. Patients who achieved culture conversion by Month 6 were continued on Arikayce plus background multidrug regimen or background multidrug regimen alone based on their randomization for a total of 12 months after the first negative sputum culture. At baseline, 329 patients were on a multidrug background regimen that included a macrolide (93.3%), a rifamycin (86.3%), or ethambutol (81.4%). The proportion of patients achieving culture conversion by Month 6 was significantly greater with Arikayce plus background multidrug regimen vs. background multidrug regimen alone (29% vs. 8.9%, respectively; $P < 0.0001$). Among patients who achieved culture conversion by Month 6, 55.4% of patients in the Arikayce group vs. no patients in the background multidrug regimen only group had sustained and durable conversion ($P = 0.0017$).[8] Relapse rates through 3 months after treatment were 9.2% in the Arikayce group vs. 30.0% in the background therapy only group.

Guidelines

The American Thoracic Society, the European Respiratory Society, the European Society of Clinical Microbiology and Infectious Disease, and the Infectious Disease Society of America developed clinical practice guidelines for the treatment of nontuberculous mycobacterial (NTM) pulmonary disease (2020).[2] Treatment recommendations for MAC lung disease are based on disease severity and previous therapies received and almost all are three drug regimens. Typical regimens involve azithromycin or clarithromycin; ethambutol; and rifampin. For select patients, a two-drug regimen consisting of azithromycin or clarithromycin plus ethambutol daily is acceptable. Liposomal amikacin is not recommended for the initial treatment of MAC pulmonary disease. The guidelines recommend the addition of liposomal amikacin to

guideline-based therapy in patients with MAC pulmonary disease who have failed treatment (failure to convert sputum culture) after ≥ 6 months of treatment with guideline-based therapy. Patients should be treated for ≥12 months after culture conversion. The breakpoint for resistance to amikacin is ≥ 64 mcg/mL for parenteral amikacin and ≥ 128 mcg/mL for amikacin liposome inhalation suspension, and finding these MICs would lead to cessation of therapy. In patients with MAC pulmonary disease, guidelines suggest susceptibility-based treatment for macrolides and amikacin over empiric therapy (conditional recommendation, very low certainty in estimates of effect).

The US Cystic Fibrosis Foundation and the European Cystic Fibrosis Society (2016 version) developed consensus recommendations on the treatment of NTM lung disease in which nebulized amikacin is listed as a treatment option for MAC and *M. abscessus* lung disease in cystic fibrosis (CF) patients.[3] The guidelines recommend that inhaled amikacin be used in conjunction with other NTM antibiotics.

Other Uses with Supportive Evidence

The efficacy of Arikayce in the treatment of *Pseudomonas aeruginosa* infection in patients with CF has been assessed in three studies.[4] In a Phase III, randomized, open-label, non-inferiority study, patients with CF were randomized to Arikayce 590 mg once daily (QD) or tobramycin inhalation solution (TIS) 300 mg twice daily (n = 302). Patients received three cycles of treatment which consisted of 28 days on treatment followed by 28 days off treatment. The primary endpoint of the study was the relative change from baseline to the end of the 24-week study in forced expiratory volume in 1 second (FEV_1). FEV_1 improvement at Day 168 with Arikayce was non-inferior to TIS (mean difference -1.31%). More patients receiving Arikayce experienced pulmonary exacerbations compared with TIS; however, fewer patients required all-cause hospitalization. Change in CF Questionnaire Revised was similar between groups at the end of each treatment course. Mean reductions in *P. aeruginosa* $\log_{10}$ CFU was similar for Arikayce and TIS at Day 28 and at Day 140.

A pooled report included 24 patients with CF and chronic *P. aeruginosa* infection from two Phase Ib/IIa pharmacokinetic/pharmacodynamic studies.[5] Patients received liposomal amikacin 500 mg QD by inhalation for 14 days. Statistically significant changes from baseline to Days 7 and 14 were seen in FEV_1, FEV_1 % predicted, and forced expiratory flow between 25% and 75% of forced vital capacity. Another report included pooled data from two dose-ranging studies (one Phase Ib/IIa and one Phase IIa) in patients with CF (n = 105) chronically infected with *P. aeruginosa*.[6] Patients received 70-, 140-, 280- or 560-mg of liposomal amikacin or placebo QD for 28 days and were followed for an additional 28 days. In repeated-measures mixed-effect models, the 560 mg dose was associated with statistically significant improvements in FEV_1, and FEV_1 % predicted and a reduction in $\log_{10}$ CFUs.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Arikayce. All approvals are provided for the duration noted below. In cases where the approval duration is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Arikayce as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Arikayce to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Arikayce is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. ***Mycobacterium avium* Complex Lung Disease.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year of the patient meets the following (i, ii, iii, iv, v, vi, and vii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has completed ≥ 6 consecutive months of a background multidrug regimen; AND
       Note: A multidrug regimen typically includes a macrolide (azithromycin or clarithromycin), ethambutol, and a rifamycin (rifampin or rifabutin).
     - **iii.** Patient has a positive sputum culture for *Mycobacterium avium* complex; AND
     - **iv.** The culture meets BOTH of the following (a and b):
       - **a)** Culture was collected within the past 3 months; AND
       - **b)** Culture was collected AFTER the patient has completed ≥ 6 consecutive months of a background multidrug regimen; AND
     - **v.** The *Mycobacterium avium* complex isolate is susceptible to amikacin, according to the laboratory report; AND
     - **vi.** The medication will be used in conjunction with a background multidrug regimen; AND
       Note: A multidrug regimen typically includes a macrolide (azithromycin or clarithromycin), ethambutol, and a rifamycin (rifampin or rifabutin).
     - **vii.** The medication is prescribed by a pulmonologist, infectious diseases physician, or a physician who specializes in the treatment of *Mycobacterium avium* complex lung infections.
   - **B)** Patient is Currently Receiving Arikayce. Approve for the duration noted below if the patient meets both of the following (i and ii):
     - **i.** The medication will be used in conjunction with a background multidrug regimen; AND
       Note: A multidrug regimen typically includes a macrolide (azithromycin or clarithromycin), ethambutol, and a rifamycin (rifampin or rifabutin).
     - **ii.** Patient meets ONE of the following (a or b):
       - **a)** Approve for 1 year if patient has not achieved negative sputum cultures for *Mycobacterium avium* complex; OR
       - **b)** Approve for 1 year (total) if patient has achieved negative sputum cultures for *Mycobacterium avium* complex for less than 12 months.
         Note: Approve enough Arikayce to complete 12 months of therapy following a negative sputum culture for *Mycobacterium avium* complex.

Other Uses with Supportive Evidence

2. **Cystic Fibrosis**. Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient has *Pseudomonas aeruginosa* in culture of the airway (e.g., sputum culture, oropharyngeal culture, bronchoalveolar lavage culture); AND
   - **B)** The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Arikayce is not recommended in the following situations:

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

19. Arikayce® suspension for oral inhalation [prescribing information]. Bridgewater, NJ: Insmed; February 2023.
20. Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: An official ATS/ERS/ESCMID/IDSA clinical practice guideline. *Eur Respir J*. 2020;56:2000535.
21. Floto RA, Olivier KN, Saiman L, et al. US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis. *Thorax*. 2016;7:i1-i22.
22. Bilton D, Pressler T, Fajac I, et al. Amikacin liposome inhalation suspension for chronic *Pseudomonas aeruginosa* infection in cystic fibrosis. *J Cyst Fibros*. 2020;19:284-291.
23. Okusanya OO, Bhavnani SM, Hammel J, et al. Pharmacokinetic and pharmacodynamic evaluation of liposomal amikacin for inhalation in cystic fibrosis patients with chronic Pseudomonal infection. *Antimicrob Agents Chemother*. 2009;53:3847-3854.
24. Okusanya OO, Bhavnani SM, Hammel JP, et al. Evaluation of the pharmacokinetics and pharmacodynamics of liposomal amikacin for inhalation in cystic fibrosis patients with chronic Pseudomonal infections using data from two Phase 2 clinical studies. *Antimicrob Agents Chemother*. 2014;58:5005-5015.
25. Griffith DE, Eagle G, Thomson R et al; for the CONVERT Study Group. Amikacin liposome inhalation suspension for treatment-refractory lung disease caused by *Mycobacterium avium* complex (CONVERT) a prospective, open-label, randomized study. *Am J Respir Crit Care Med*. 2018;198(12):1559-1569.
26. Griffith DE, Thomson R, Flume P et al; for the CONVERT Study Group. Amikacin liposome inhalation suspension for refractory *Mycobacterium avium* complex lung disease. *Chest*. 2021;160(3):831-842.

PRIOR AUTHORIZATION POLICY

POLICY: Antibiotics (Inhaled) – Cayston Prior Authorization Policy
- Cayston® (aztreonam inhalation solution – Gilead)

REVIEW DATE: 03/29/2023

OVERVIEW

Cayston, a monobactam antibiotic, is indicated to improve respiratory symptoms in **cystic fibrosis** (CF) patients with *Pseudomonas aeruginosa*.[1] Safety and efficacy have not been established in pediatric patients < 7 years of age, in patients with forced expiratory volume in 1 second (FEV_1) < 25% or > 75% predicted, or in patients colonized with *Burkholderia cepacia*.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cayston and other antibiotics, Cayston should be used to treat patients with CF known to have *P. aeruginosa* in the lungs.[1]

Clinical Efficacy

An open-label study assessed inhaled aztreonam for the eradication of newly acquired *P. aeruginosa* in children aged 3 months to < 18 years of age (n = 105).[2] In total, 49 patients < 6 years of age were included in the study. Patients received inhaled aztreonam 75 mg three times daily for 28 days. At the end of treatment with inhaled aztreonam, 91.5% of the patients (n = 43/47) < 6 years of age were culture-negative for *P. aeruginosa* and 76.6% of patients (n = 36/47) < 6 years of age remained culture-negative 4 weeks after completing the course of therapy.

Guidelines

The Cystic Fibrosis Foundation (CFF) Pulmonary Therapeutics Committee provides recommendations for the use of chronic medications in the management of CF lung disease (2013).[3] In patients ≥ 6 years of age with CF and moderate-to-severe lung disease with *P. aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled aztreonam is strongly recommended to improve lung function and quality of life (QoL). For mild disease, the Committee recommends chronic use of inhaled aztreonam for patients ≥ 6 years of age with CF and *P. aeruginosa* persistently present in cultures of the airways, to improve lung function and QoL.

The CFF published a systematic review of the literature regarding eradication of initial *P. aeruginosa* infections to develop guidelines for effective prevention (2014).[4] The recommendations pertaining to inhaled antibiotics are as follows: 1) Inhaled antibiotic therapy is recommended for the treatment of initial or new growth of *P. aeruginosa* (the favored antibiotic regimen is tobramycin [300 mg twice daily {BID}] for 28 days); and 2) Prophylactic antipseudomonal antibiotics to prevent the acquisition of *P. aeruginosa* are not recommended.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cayston. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cayston as well as the monitoring required for adverse events and long-term efficacy, approval requires Cayston to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cayston is recommended in those who meet one of the following criteria:

FDA-Approved Indication

3. Cystic Fibrosis. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient has *Pseudomonas aeruginosa* in culture of the airway; AND
  Note: Examples of culture of the airway include sputum culture, oropharyngeal culture, bronchoalveolar lavage culture.
- **B)** The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

Other Uses with Supportive Evidence

4. Continuation of Cayston. Approve for 1 month if the patient was started on Cayston and is continuing a course of therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cayston is not recommended in the following situations:

7. Nasal Rinse. Cayston is not approvable for compounding of aztreonam nasal rinse.

8. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

27. Cayston® inhalation solution [prescribing information]. Foster City, CA: Gilead; November 2019.
28. Tiddens HAWM, De Boeck K, Clancy JP, et al. Open label study of inhaled aztreonam for *Pseudomonas* eradication in children with cystic fibrosis: The ALPINE study. *J Cyst Fibros*. 2015;14:111-119.
29. Mogayzel PJ, Naureckas ET, Robinson KA, et al. Cystic Fibrosis Pulmonary Guidelines. Chronic Medications for Maintenance of Lung Health. *Am J Respir Crit Care Med*. 2013;187:680-689.
30. Mogayzel PJ, Naureckas ET, Robinson KA, et al; and the Cystic Fibrosis Foundation Pulmonary Clinical Practice Guidelines Committee. Pharmacologic approaches to prevention and eradication of initial *Pseudomonas aeruginosa* infection. *Ann Am Thorac Soc*. 2014;11(10):1640-1650.

PRIOR AUTHORIZATION POLICY

POLICY: Antibiotics (Inhaled) – TOBI Podhaler Prior Authorization Policy
- TOBI® Podhaler (tobramycin inhalation powder – Novartis)

REVIEW DATE: 03/29/2023

OVERVIEW

TOBI Podhaler, an aminoglycoside antibiotic, is indicated for the management of **cystic fibrosis** (CF) patients with *Pseudomonas aeruginosa*.[1] Safety and efficacy have not been demonstrated in patients < 6 years of age, patients with forced expiratory volume in 1 second (FEV_1) < 25% or > 80% predicted, or patients colonized with *Burkholderia cepacia.*

Guidelines

The Cystic Fibrosis Foundation (CFF) Pulmonary Therapeutics Committee (2013) provides recommendations for the use of chronic medications in the management of CF lung disease.[2] In patients ≥ 6 years of age with CF and moderate-to-severe lung disease with *P. aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled tobramycin is strongly recommended to improve lung function, quality of life, and reduce exacerbations. For mild disease, the Committee recommends chronic use of inhaled tobramycin for patients ≥ 6 years of age with CF and *P. aeruginosa* persistently present in cultures of the airways, to reduce exacerbations.

The CFF published a systematic review of the literature regarding eradication of initial *P. aeruginosa* infections to develop guidelines for effective prevention (2014).[3] The recommendations pertaining to inhaled antibiotics are as follows: 1) Inhaled antibiotic therapy is recommended for the treatment of initial or new growth of *P. aeruginosa* (the favored antibiotic regimen is tobramycin [300 mg twice daily {BID}] for 28 days); and 2) Prophylactic antipseudomonal antibiotics to prevent the acquisition of *P. aeruginosa* are not recommended.

The American Thoracic Society (ATS) published a clinical review (2013) of non-cystic fibrosis bronchiectasis on their webpage.[4] The review lists nebulized antibiotics (e.g., colistin, gentamicin, tobramycin) as treatment options for the eradication or suppression of *P. aeruginosa*. The European Respiratory Society (ERS) have published guidelines (2017) for the management of adult bronchiectasis and recommend patients with a new isolate of *P. aeruginosa* be offered eradication antibiotic treatment which includes nebulized antibiotics (e.g., colistin, gentamicin, tobramycin).[5] Neither the ATS nor the ERS guidelines include Tobi Podhaler® (tobramycin inhalation powder) as a treatment option for bronchiectasis and no clinical trials have been published with Tobi Podhaler for treatment of non-cystic fibrosis bronchiectasis.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of TOBI Podhaler. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with TOBI Podhaler as well as the monitoring required for adverse events and long-term efficacy, approval requires TOBI Podhaler to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of TOBI Podhaler is recommended in those who meet one of the following criteria:

FDA-Approved Indication

5. Cystic Fibrosis. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 6 years of age; AND
- **B)** Patient has *Pseudomonas aeruginosa* in culture of the airway; AND
  Note: Examples of culture of the airway include sputum culture, oropharyngeal culture, bronchoalveolar lavage culture.
- **C)** The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

Other Uses with Supportive Evidence

6. Continuation of TOBI Podhaler. Approve for 1 month if the patient was started on TOBI Podhaler and is continuing a course of therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of TOBI Podhaler is not recommended in the following situations:

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

31. TOBI® Podhaler inhalation powder [prescribing information]. East Hanover, NJ: Novartis; February 2023.
32. Mogayzel PJ, Naureckas ET, Robinson KA, et al. Cystic Fibrosis Pulmonary Guidelines. Chronic Medications for Maintenance of Lung Health. *Am J Respir Crit Care Med*. 2013;187:680-689.
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34. McShane PJ, Naureckas ET, Tino G, Strek ME. Non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med*. 2013;188:647-656.
35. Polverino E, Goeminne PC, McDonnell, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J*. 2017;50:1700629.

PRIOR AUTHORIZATION POLICY

POLICY: Antibiotics (Inhaled) – Tobramycin Inhalation Solution Prior Authorization Policy
- Bethkis® (tobramycin inhalation solution – Chiesi)
- Kitabis® (tobramycin inhalation solution – Pari, authorized generic)
- TOBI® (tobramycin inhalation solution – Mylan, generic)

REVIEW DATE: 03/29/2023

OVERVIEW

TOBI, Kitabis, and Bethkis, tobramycin inhalation solutions, are aminoglycoside antibiotics indicated for the management of **cystic fibrosis (CF)** in patients with *Pseudomonas aeruginosa*.[1-3] TOBI and Kitabis are indicated for the management of CF in patients ≥ 6 years of age.[1,2] Safety and efficacy have not been demonstrated in patients < 6 years of age, patients with forced expiratory volume in 1 second (FEV_1) < 25% or > 75% predicted, or patients colonized with *Burkholderia cepacia*. Bethkis is indicated for the management of CF patients with *P. aeruginosa*.[3] Safety and efficacy have not been demonstrated in patients < 6 years of age, patients with FEV_1 < 40% or > 80% predicted, or patients colonized with *B. cepacia*.

Guidelines

The Cystic Fibrosis Foundation (CFF) Pulmonary Therapeutics Committee published recommendations for the use of chronic medications in the management of CF lung disease (2013).[4] In patients ≥ 6 years of age with CF and moderate-to-severe lung disease with *P. aeruginosa* persistently present in cultures of the airways, chronic use of inhaled tobramycin is strongly recommended to improve lung function, quality of life and reduce exacerbations. For mild disease, the Committee recommends chronic use of inhaled tobramycin for patients ≥ 6 years of age with CF and *P. aeruginosa* persistently present in cultures of the airways, to reduce exacerbations.

The CFF published a systematic review of the literature regarding eradication of initial *P. aeruginosa* infections to develop guidelines for effective prevention (2014).[5] The recommendations pertaining to inhaled antibiotics are as follows: 1) Inhaled antibiotic therapy is recommended for the treatment of initial or new growth of *P. aeruginosa* (the favored antibiotic regimen is tobramycin [300 mg twice daily {BID}] for 28 days); and 2). Prophylactic antipseudomonal antibiotics to prevent the acquisition of *P. aeruginosa* are not recommended.

Other Uses with Supportive Evidence

A few trials support the efficacy of tobramycin inhalation solution (TIS) for the treatment of bronchiectasis with *P. aeruginosa* infection. A literature review concluded that in patients with non-CF bronchiectasis and chronic *P. aeruginosa* infection, TIS is effective in reducing the density of bacteria in sputum, which may be associated with additional clinical benefit.[12]

In a randomized, double-blind, placebo-controlled study, patients received either TIS 300 mg (n = 37) or placebo (n = 37) (BID for 4 weeks and were followed for an additional 2 weeks off treatment.[6] At Week 4, the TIS group had a mean 4.54 $\log_{10}$ decrease in *P. aeruginosa* colony-forming units (CFU)/g of sputum compared with no change in the placebo group (P < 0.01). At Week 6, complete eradication of *P. aeruginosa* occurred in 35% of the patients in the TIS group compared with none in the placebo group, and 62% of patients in the TIS group vs. 38% of patients in the placebo group had improvements in their general health (odds ratio 2.7; 95% confidence interval: 1.1, 6.9).

In a randomized, single-blind study, patients received TIS 300 mg (n = 16) or placebo (n = 19) BID for 3 months following a 14-day course of intravenous ceftazidime and tobramycin and were followed for an additional 12 months.[7] At the end of the study, 54.5% of patients in the TIS group (n = 6/11) and 29.4% of patients in the placebo group (n = 5/17) were free of *P. aeruginosa* (P = 0.048). In addition, patients in the TIS group had significantly fewer exacerbations (1.27 vs. 2.5; P = 0.044), hospital admissions (0.06 vs. 0.47; P = 0.037), and hospital days (0.9 vs. 13.56; P = 0.034) than patients in the placebo group, respectively. No significant differences were found in pulmonary function tests.

A double-blind, placebo-controlled, crossover study randomized 30 patients to initial TIS 300 mg or placebo BID for 6 months, followed by a 1 month washout period and 6 months of therapy with the other treatment.[8] During the first treatment period, TIS treatment resulted in a significant reduction in *P. aeruginosa* density compared with placebo (P = 0.038). During both treatment periods, patients treated with TIS had fewer hospital admissions (0.15 vs. 0.75; P = 0.038) and hospital days (2.05 vs. 12.65; P = 0.047) than patients treated with placebo, respectively. No significant changes in the number of exacerbations and/or pulmonary function tests were observed.

In an open-label trial, 41 patients received three cycles of TIS 300 mg BID for 14 days followed by 14 days off therapy.[9] Patients were followed for an additional 40 weeks after the three cycles of treatment with TIS. At Week 10, there was a significant improvement from baseline (mean change 1.5 points; P = 0.006) in the composite pulmonary symptom score which included cough, shortness of breath, sputum production, fatigue, and wheezing. Quality of life, assessed using the St. George's Respiratory Questionnaire, was significantly improved at Week 10 (mean change 9.8; P < 0.001) compared with baseline. At Week 12, 22.2% of patients (n = 6/27) were considered to have *P. aeruginosa* eradicated from sputum cultures.

A Phase III, multicenter, double-blind, placebo-controlled trial randomized adults with symptomatic bronchiectasis with positive *P. aeruginosa* sputum culture to TIS 300 mg (n = 167) or placebo (n = 172) in addition to standard of care.[13] Treatment was provided for two cycles, each consisting of 28 days on therapy and 28 days off therapy. At Week 16, there was a significant reduction in *P. aeruginosa* density with TIS vs. placebo (adjusted difference 1.74 $\log_{10}$ CFU/g; P < 0.001) and a greater improvement in the quality of life bronchiectasis respiratory symptom score on Day 29 (adjusted mean difference 7.91; P < 0.001). Significantly more patients were culture negative for *P. aeruginosa* in the TIS group vs. placebo on Day 29 (29.3% vs. 10.6%, respectively).

The American Thoracic Society (ATS) published a clinical review (2013) of non-cystic fibrosis bronchiectasis.[10] The review lists nebulized antibiotics (e.g., colistin, gentamicin, tobramycin) as treatment options for the eradication or suppression of *P. aeruginosa*. The European Respiratory Society (ERS) have published guidelines (2017) for the management of adult bronchiectasis and recommend patients with a new isolate of *P. aeruginosa* be offered eradication antibiotic treatment which includes nebulized antibiotics (e.g., colistin, gentamicin, tobramycin).[11] While both the ATS and ERS list nebulized colistin and gentamicin as treatment options for non-cystic fibrosis bronchiectasis, neither drug has a commercially available formulation for nebulization.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of tobramycin inhalation solution. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with tobramycin inhalation solution as well as the monitoring required for adverse events and long-term efficacy, approval requires tobramycin inhalation solution to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of tobramycin inhalation solution is recommended in those who meet one of the following criteria:

FDA-Approved Indication

7. **Cystic Fibrosis.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient has *Pseudomonas aeruginosa* in culture of the airway; AND
     Note: Examples of culture of the airway include sputum culture, oropharyngeal culture, bronchoalveolar lavage culture.
   - **B)** The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

Other Uses with Supportive Evidence

8. **Bronchiectasis, Non-Cystic Fibrosis**. Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has *Pseudomonas aeruginosa* in culture of the airway; AND
     Note: Examples of culture of the airway include sputum culture, oropharyngeal culture, bronchoalveolar lavage culture.
   - **C)** The medication is prescribed by or in consultation with a pulmonologist.

9. **Continuation of Tobramycin Inhalation Solution Therapy**. Approve for 1 month if the patient was started on tobramycin inhalation solution and is continuing a course of therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of tobramycin inhalation solution is not recommended in the following situations:

10. **Nasal Rinse**. Tobramycin inhalation solution is not approvable for compounding of tobramycin nasal rinse.

11. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Antibiotics (Injectable) Prior Authorization Policy

REVIEW DATE: 09/20/2023

Note: This list is not all-inclusive.

OVERVIEW

Injectable antibiotics are used to treat moderate to severe bacterial infections.[1] In addition, injectable antibiotics can be used for prophylactic indications (e.g., before surgeries; in immunocompromised patients [e.g., patients with cancer]).

Recently, some injectable antibiotics are being used with nasal or nebulized corticosteroids to compound nasal rinses and nasal irrigations. There are no data to support the use of these products in this manner.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of the injectable antibiotics listed above, when these products are prescribed in conjunction with nasal or nebulized dosage forms of beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone, or triamcinolone. The list of injectable antibiotics in this policy is not inclusive; other injectable antibiotics may also be targeted in this policy. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: This Prior Authorization policy will apply to injectable antibiotics when there is a prescription history of a nasal or nebulized formulation of the selected corticosteroid (beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone, triamcinolone) in the past 180 days. Prescriptions for injectable antibiotics without a claims for nasal or nebulized corticosteroids in the past 180 days are excluded from the Prior Authorization policy.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of injectable antibiotics is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Systemic Bacterial Infections (Prophylaxis or Treatment).** Approve for 3 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of injectable antibiotics is not recommended in the following situations:

16. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Facts and Comparisons® Online. Wolters Kluwer Health, Inc.; 2023. Available at: http://online.factsandcomparisons.com/login.aspx?url=/index.aspx&qs=. Accessed on September 15, 2023. Search terms: aminoglycoside, carbapenem, cephalosporin, glycopeptide, lincosamide, macrolide, oxazolidione, penicillin, quinolone, tetracycline.

PRIOR AUTHORIZATION POLICY

POLICY: Antibiotics – Linezolid (Zyvox), Sivextro Prior Authorization Policy
- Zyvox® (linezolid tablets and oral suspension – Pfizer, generic)
- Sivextro™ (tedizolid phosphate tablets – Cubist Pharmaceuticals)

REVIEW DATE: 12/06/2023

OVERVIEW

Linezolid (Zyvox) and Sivextro are synthetic oxazolidinone antimicrobial agents.[1-2] Both agents have clinical utility in the treatment of infections caused by aerobic Gram-positive bacteria. Cross-resistance between linezolid or Sivextro and other classes of antibiotics is unlikely because the mechanism of action for both of these agents differs from that of other antibacterial agents.

Linezolid is indicated in adults and children for the treatment of the following infections caused by susceptible strains of the designated microorganisms:[1]
- **Community-acquired pneumonia** (CAP), caused by *Streptococcus pneumoniae*, including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible [MSSA] only);
- **Complicated skin and skin structure infections** (SSTIs), including diabetic foot infections, without concomitant osteomyelitis caused by *S. aureus* (MSSA and methicillin-resistant [MRSA]), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. Zyvox has not been studied in the treatment of decubitus ulcers;
- **Nosocomial pneumonia**, caused by *S. aureus* (MSSA and MRSA), or *S. pneumoniae*;
- **Uncomplicated SSTIs**, caused by *S. aureus* (MSSA only) or *S. pyogenes*;
- **Vancomycin-resistant *Enterococcus faecium* infections**, including cases with concurrent bacteremia.

Limitation of Use: Zyvox is not indicated for the treatment of Gram-negative infections. It is crucial that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected. The safety and efficacy of Zyvox formulations given longer than 28 days have not been evaluated in controlled clinical trials.

Sivextro is indicated for the treatment of **acute bacterial skin and skin structure infections** (ABSSSI) in adults and pediatric patients ≥ 12 years of age that are caused by susceptible isolates of the following Gram-positive microorganisms: *S. aureus* (MRSA and MSSA), *S. pyogenes*, *S. agalactiae*, *Streptococcus anginosus* Group (including *S. anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*), and *Enterococcus faecalis*.[2]

Although linezolid and Sivextro are indicated for susceptible strains of MSSA and drug-resistant strains of *S. pneumoniae* in some situations, it is not the optimal drug or drug of first-choice for these microorganisms.[3-4] Other antibiotics may be used. In efforts to reduce the development of drug-resistant bacteria and maintain effectiveness of linezolid and Sivextro, both antibiotics should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.[1,2] When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Guidelines

Linezolid and Sivextro are addressed in a number of Infectious Disease Society of America (IDSA) guidelines:

- ***Diabetic Foot Infections:*** A clinical practice guideline for the diagnosis and treatment of diabetic foot infections (2023) notes that diabetic foot infections of moderate severity may be treated with oral or initial parenteral therapy, while severe infections should be treated with parenteral therapy.[6] Linezolid, Cubicin® (daptomycin injection), doxycycline, clindamycin, fluoroquinolones and intravenous (IV) vancomycin are listed as therapy options for infections caused by MRSA.
- ***Infective Endocarditis:*** Treatment guidelines, from the American Heart Association and endorsed by the IDSA (2015), recommend linezolid as a treatment option for patients with infective endocarditis caused by *Enterococcus* species that is resistant to penicillin, aminoglycosides, and vancomycin.[9]
- ***MRSA:*** Guidelines (2011) for the treatment of MRSA infections recognize linezolid as a treatment option for other infections including infections of the central nervous system (e.g., meningitis, brain abscess), osteomyelitis, and septic arthritis.[5]
- ***Pneumonia:*** Guidelines from the American Thoracic Society (ATS) and IDSA (2016) recommend that MRSA hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP) be treated with either vancomycin or linezolid rather than other antibiotics or other antibiotic combinations.[4] The choice between vancomycin and linezolid may be guided by patient-specific factors such as blood cell counts, concurrent prescriptions for serotonin-reuptake inhibitors, renal function, and cost. The available evidence indicates that vancomycin and linezolid are roughly similar and no alternative agent or regimen is clearly superior to these two products. Guidelines from the IDSA/ATS (2019) for CAP recommend vancomycin or linezolid for the treatment of community-acquired MRSA.[3] In addition, the Pediatric Infectious Disease Society and the IDSA guidelines (2011) for the treatment of CAP in infants and children > 3 months of age recommend linezolid as an alternative to vancomycin for treatment of MRSA, and as an alternative to ceftriaxone for the treatment of *S. pneumoniae* resistant to penicillin.[8]
- ***SSTIs:*** Guidelines (2014) for the diagnosis and management of SSTIs, for mild nonpurulent (i.e., necrotizing infection, cellulitis, erysipelas) SSTI, recommend oral antibiotics such as penicillin VK, cephalosporin, dicloxacillin, or clindamycin.[7] For moderate nonpurulent SSTI, IV antibiotics such as penicillin, ceftriaxone, cefazolin, or clindamycin are recommended. For moderate purulent SSTIs, empiric treatment can be started with trimethoprim/sulfamethoxazole (TMP/SMX) or doxycycline. For MRSA infections, TMP/SMX is the recommended therapy. Cephalexin or dicloxacillin are usually effective for MSSA infections. For severe purulent SSTI, empiric therapy with IV vancomycin, Cubicin, linezolid, Vibativ® (telavancin intravenous infusion), or Teflaro® (ceftaroline intravenous infusion) are recommended. All of these agents are active against MRSA strains. For severe purulent SSTI caused by MSSA, therapy can be switched to nafcillin, cefazolin, or clindamycin.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of linezolid and Sivextro. All approvals are provided for the duration noted below. In cases where approval is in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of linezolid is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Methicillin-Resistant *Staphylococcus* Species Infection, Treatment**. Approve for 1 month.

2. **Vancomycin-Resistant *Enterococcus* Species Infection, Treatment**. Approve for 1 month.

Other Uses with Supportive Evidence

3. **Continuation of Linezolid Therapy.** Approve for 1 month in patients who meet ONE of the following (A or B):
   A) Patient is transitioning from intravenous (IV) linezolid or IV vancomycin to oral linezolid therapy; OR
   B) Patient was started on oral linezolid in an inpatient facility and is continuing therapy.

4. **Treatment of an Infection that is Resistant to Other Antibiotics, but the Organism is Sensitive to Linezolid.** Approve for 1 month.

5. **There is Insufficient Information Available to Make a Determination Regarding Coverage and the Prescriber or Representative Cannot be Contacted.** Approve for up to 2 weeks of therapy.

   To avoid delays or disruption in therapy for the patient, if there is insufficient information available to make a determination regarding coverage and the prescriber or representative of the prescriber cannot be contacted, approve linezolid for up to 2 weeks.

II. Coverage of Sivextro is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. **Acute Bacterial Skin and Skin Structure Infections (ABSSSI) Caused by Methicillin-Resistant *Staphylococcus aureus* (MRSA), Selected *Streptococcus* Species (i.e., *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus anginosus* Group) and *Enterococcus faecalis*.** Approve for up to 6 days of therapy.

Other Uses with Supportive Evidence

2. **Continuation of Sivextro Therapy in the Outpatient Setting.** Approve for up to 6 days of therapy in patients transitioning from Sivextro IV therapy to oral therapy.

3. **There is Insufficient Information Available to Make a Determination Regarding Coverage and the Prescriber or Representative Cannot be Contacted.** Approve for up to 6 days of therapy.

   To avoid delays or disruption in therapy for the patient, if there is insufficient information available to make a determination regarding coverage and the prescriber or representative of the prescriber cannot be contacted, approve Sivextro. Since the available data for Sivextro only supports up to 6 days of therapy for the ABSSSI indication, we are limiting approval to this duration.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of linezolid and Sivextro is not recommended in the following situations:

17. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria for both linezolid and Sivextro. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Antibiotics – Synercid Prior Authorization Policy
- Synercid® (quinupristin and dalfopristin intravenous infusion – Pfizer)

REVIEW DATE: 07/12/2023

OVERVIEW

Synercid is indicated in adults for the treatment of **complicated skin and skin structure infections** caused by *Staphylococcus aureus* (methicillin-susceptible) or *Streptococcus pyogenes*.[1] To reduce the development of drug-resistant bacteria and maintain effectiveness of Synercid, it should only be used to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

Guidelines

According to the Infectious Diseases Society of America (IDSA) guidelines for the diagnosis and management of skin and soft tissue infections (SSTIs) [2014], oral antibiotics such as penicillin VK, cephalosporin, dicloxacillin, and clindamycin can be used for mild nonpurulent SSTI (i.e., necrotizing infection, cellulitis, erysipelas).[2] For moderate nonpurulent SSTI, intravenous (IV) antibiotics such as penicillin, ceftriaxone, cefazolin, and clindamycin are recommended. For moderate purulent SSTIs, empiric treatment can be started with trimethoprim/sulfamethoxazole (TMP/SMX) or doxycycline. For methicillin-resistant *Staphylococcus aureus* (MRSA) infections, TMP/SMX is the recommended therapy. Cephalexin or dicloxacillin are usually effective for methicillin-susceptible *Staphylococcus aureus* (MSSA) infections. For severe purulent SSTI, empiric therapy with vancomycin (IV), daptomycin, linezolid, Vibativ® (telavancin intravenous infusion), or Teflaro® (ceftaroline intravenous infusion) are recommended. All of these agents are active against MRSA strains. For severe purulent SSTI caused by MSSA, therapy can be switched to nafcillin, cefazolin, or clindamycin. Synercid is recommended as an alternative in patients with severe penicillin hypersensitivity for the treatment of necrotizing infections of the skin, fascia, and muscle.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Synercid. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Synercid is recommended in those who meet one of the following criteria:

FDA-Approved Indication

10. Skin and Skin Structure Infections, Complicated. Approve for 1 month if the patient meets the following (A and B):
- **A)** Patient has an infection that is proven or strongly suspected to be caused by *Staphylococcus aureus* (methicillin-susceptible) or *Streptococcus pyogenes*; AND
- **B)** Patient has severe penicillin hypersensitivity.

Other Uses with Supportive Evidence

11. **Treatment of an Infection Caused by a Susceptible Microorganism**. Approve for 1 month if the patient meets the following (A and B):
    A) The microorganism is resistant to two other antibiotics; AND
    B) The microorganism is sensitive to Synercid.

12. **Continuation of Synercid Therapy.** Approve for 1 month if the patient meets the following (A and B):
    A) Patient was started on Synercid; AND
    B) Patient is continuing a course of therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Synercid is not recommended in the following situations:

12. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

49. Synercid® for injection [prescribing information]. New York, NY: Pfizer; July 2018.
50. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2014;59:e10-e52.

PRIOR AUTHORIZATION POLICY

POLICY: Antibiotics – Vancomycin Capsules Prior Authorization Policy
- Vancocin® (vancomycin capsules – Ani Pharmaceuticals, generic)

REVIEW DATE: 08/23/2023

OVERVIEW

Vancomycin capsules, an antimicrobial, are indicated for the following uses:[1]
- ***Clostridiodes difficile*-** (formerly known as *Clostridium difficile)* **associated diarrhea**.
- **Enterocolitis** caused by ***Staphylococcus aureus*** (including methicillin-resistant strains).

The usual duration of therapy for the treatment of *C. difficile*-associated diarrhea in adults is 10 days and for pediatric patients (< 18 years of age), the duration is typically 7 to 10 days.[1] The usual duration of therapy for the treatment of Staphylococcal enterocolitis is 7 to 10 days.

Recently, vancomycin capsules are being used in conjunction with one or more of the following topical products: clindamycin, clotrimazole, ketoconazole, or mupirocin to compound foot baths or other topical products. There are no data to support such use.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of vancomycin capsules when being prescribed in conjunction with one or more of the following: topical clindamycin products, topical clotrimazole products, topical ketoconazole products, and/or topical mupirocin products. All approvals are provided for the duration noted below.

Automation: This Prior Authorization policy will apply to vancomycin capsules when there is a prescription history of topical clindamycin products, topical clotrimazole products, topical ketoconazole products, and/or topical mupirocin products in the past 180 days. Prescriptions for vancomycin capsules without a claims for topical clindamycin, topical clotrimazole, topical ketoconazole, and/or topical mupirocin products in the past 180 days are excluded from the Prior Authorization policy.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of vancomycin capsules is recommended in those who meet one of the following criteria:

FDA-Approved Indications

2. ***Clostridiodes Difficile* – Associated Diarrhea.** Approve for 2 weeks.

3. **Enterocolitis – Caused by *Staphylococcus aureus*.** Approve for 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of vancomycin capsules is not recommended in the following situations.

18. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

2. Vancocin® capsules [prescribing information]. Baudette, MN: Ani Pharmaceuticals; January 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Antibiotics – Xifaxan Prior Authorization Policy
- Xifaxan® (rifaximin tablets – Salix)

REVIEW DATE: 12/06/2023

OVERVIEW

Xifaxan, a rifamycin antibiotic, is indicated for the following uses:[1]
- **Hepatic encephalopathy (HE)**, to reduce the risk of overt disease in adults.
- **Irritable bowel syndrome with diarrhea (IBS-D)**, in adults.
- **Travelers' diarrhea (TD)**, caused by noninvasive *Escherichia coli* in patients ≥ 12 years of age.

Limitations of Use: TD: Xifaxan should not be used in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than *E. coli*.[1]

In the trials of Xifaxan for HE, 91% of the patients were using lactulose concomitantly.[1] Due to small sample size, differences in the treatment effect of those patients not using lactulose concomitantly could not be assessed. Data are lacking to support the use of Xifaxan without concomitant use of lactulose.

Guidelines

- **Hepatic Encephalopathy**: The European Association for the Study of the Liver (EASL) guidelines for HE (2022) recommend Xifaxan as an adjunct to lactulose as secondary prophylaxis following ≥ 1 additional episode of overt HE within 6 months of the first episode.[2] Guidelines also state that in patients with cirrhosis and previous episodes of overt HE, Xifaxan can be considered for prophylaxis of HE prior to non-urgent transjugular intrahepatic portosystemic shunt (TIPS) placement.
- **IBS with Diarrhea**: The American College of Gastroenterology (ACG) guidelines for the management of IBS (2021) suggest Xifaxan to reduce the global symptoms of IBS and to reduce bloating in non-constipated IBS patients.[3] In addition, the American Gastroenterological Association (AGA) guidelines on the management of IBS-D (2022) suggest Xifaxan over no drug treatment for patients with IBS-D (conditional recommendation, moderate evidence).[4]
- **Small Intestine Bacterial Overgrowth (SIBO):** Clinical guidelines from the ACG (2020) and the AGA (2020) list Xifaxan as an option for the treatment of SIBO.[9,10] ACG also states that the diagnosis of SIBO can be made with breath testing (glucose hydrogen or lactulose hydrogen), or by small bowel aspiration and culture. Of note, in clinical trials, patients were treated with Xifaxan for a 7-day course for SIBO.[5-8]
- **Travelers' Diarrhea**: The Centers for Disease Control and Prevention Yellow Book – Health Information for International Travel (2024) states that Xifaxan may be used for the treatment of moderate, noninvasive travelers' diarrhea and may be used for the treatment of severe, non-dysenteric travelers' diarrhea.[11] In addition, guidelines developed by an expert panel (2017) state that Xifaxan is appropriate for moderate or severe, non-dysenteric travelers' diarrhea, and when indicated for the prophylaxis of travelers' diarrhea.[12]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Xifaxan. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xifaxan is recommended in those who meet one of the following criteria:

FDA-Approved Indications

13. Hepatic Encephalopathy. Approve Xifaxan 550 mg tablets for 6 months if the patient meets ALL of the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** According to the prescriber, the patient has previously had overt hepatic encephalopathy; AND
- **C)** Patient meets ONE of the following criteria (i or ii):
  - **i.** Xifaxan will be used concomitantly with lactulose; OR
  - **ii.** According to the prescriber, the patient has a contraindication or significant intolerance to treatment with lactulose.

14. Irritable Bowel Syndrome with Diarrhea. Approve Xifaxan 550 mg tablets for 14 days if the patient is ≥ 18 years of age.

15. Travelers' Diarrhea. Approve Xifaxan 200 mg tablets for 3 days if the patient meets ALL of the following (A, B, and C):
- **A)** Patient is ≥ 12 years of age; AND
- **B)** According to the prescriber, the patient is afebrile; AND
- **C)** According to the prescriber, the patient does not have blood in the stool.

Other Uses with Supportive Evidence

4. Small Intestine Bacterial Overgrowth. Approve Xifaxan (either strength) for 14 days if small intestine bacterial overgrowth is diagnosed by ONE of the following (A, B, or C):
- **A)** Glucose hydrogen breath test; OR
- **B)** Lactulose hydrogen breath test; OR
- **C)** Small bowel aspiration and culture.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xifaxan is not recommended in the following situations:

13. *Helicobacter pylori* Infection. The ACG guidelines for the treatment of *H. pylori* do not address the use of Xifaxan.[13] There are limited trials assessing the efficacy of Xifaxan in the treatment of *H. pylori* infection in adults; the available studies are small, of poor quality, and not conducted in the United States. More data are needed to define the place in therapy of rifaximin in the treatment of *H. pylori*.

14. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Anticoagulants – Dabigatran Prior Authorization Policy
- Pradaxa® (dabigatran etexilate mesylate capsules – Boehringer Ingelheim, generic)
- Pradaxa® Oral Pellets (dabigatran etexilate oral pellets – Boehringer Ingelheim)

REVIEW DATE: 01/11/2023; selected revision 04/05/2023

OVERVIEW

Dabigatran capsules (Pradaxa, generic), a direct thrombin inhibitor, is indicated for the following uses:[1]
- **Non-valvular atrial fibrillation**, to reduce the risk of stroke and systemic embolism in adults.
- **Prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE)**, in adults who have undergone hip replacement surgery.
- **Treatment of DVT and PE** in adults who have been treated with a parenteral anticoagulant for 5 to 10 days, as well as **reduction in the risk of recurrence of DVT and PE** in patients who have been previously treated.
- **Treatment of venous thromboembolic events (VTE)**, in pediatric patients 8 to < 18 years of age who have been treated with a parenteral anticoagulant for at least 5 days, as well as **to reduce the risk of recurrence of VTE** in pediatric patients 8 to < 18 years of age who have been previously treated.

Pradaxa oral pellets, a direct thrombin inhibitor, is indicated for the following uses:[15]
- **VTE**, treatment in pediatric patients 3 months of age to < 12 years of age who have been treated with a parenteral anticoagulant for at least 5 days, as well as **to reduce the risk of recurrence of VTE** in pediatric patients 3 months to < 12 years of age who have been previously treated.

It is noted in the prescribing information for dabigatran capsules and Pradaxa oral pellets that not all dosage forms are approved for the same indications and age groups.[1,15] Due to differences in bioavailability, the individual products are not substitutable on a mg-per-mg basis. Dabigatran capsules are available in the following strengths: 75 mg, 110 mg, and 150 mg. Pradaxa oral pellets are available in the following strengths per packet: 20 mg, 30 mg, 40 mg, 50 mg, 110 mg, and 150 mg.

Guidelines

Guidelines are available which support the use of direct oral anticoagulants (DOACs) in their commonly used clinical settings, such as DVT/PE[2-5] and atrial fibrillation[6,7]. In patients who are eligible for a DOAC, these are generally preferred over vitamin K antagonists (e.g., warfarin). It is noted that in the randomized trials in atrial fibrillation, DOACs were consistently at least non-inferior to warfarin regarding the composite of stroke or systemic embolism and were associated with lower risk of serious bleeding.[7]

Anticoagulants and Coronavirus Disease 19 (COVID-19)

Several clinical practice guidelines have been published with regard to use of anticoagulant therapy in the management of COVID-19. Per National Institutes of Health treatment guidelines regarding antithrombotic therapy in patients with COVID-19 (updated December 28, 2022), hospitalized patients with COVID-19 should not be routinely discharged from the hospital while on VTE prophylaxis.[8] For patients at low risk for bleeding and high risk for VTE, continuing anticoagulation with an FDA-approved regimen for extended VTE prophylaxis may be considered, as per protocols for patients without COVID-19. Of note, Xarelto® (rivaroxaban tablets) is FDA-approved for prophylaxis of VTE in acutely ill medical patients; dabigatran is not indicated in this setting. Other guidelines have similar recommendations.[9-11]

Other Uses with Supportive Evidence

Dabigatran has data supporting its use in prophylaxis after knee replacement surgery; these data are limited to adults.[12-14] Although data are not robust regarding use of DOACs in other off-label thromboembolic-related conditions, CHEST guidelines (2012) suggest anticoagulation for certain patients with superficial vein thrombosis, symptomatic splanchnic thromboses (portal, mesenteric, and/or splenic vein), or symptomatic hepatic vein thrombosis.[2] The guidelines acknowledge the limited available data in these settings, and all are given Grade 2C recommendations (weak recommendation, low-quality evidence). The 2016 CHEST guideline update did not address these conditions or comment on the role of DOACs.[3] The choice of anticoagulant is often individualized based on patient-specific factors; therefore, for certain patients, DOAC use may be considered in practice. Evidence for DOACs is limited for off-label scenarios; in general, agents such as vitamin K antagonists (e.g., warfarin) and low molecular weight heparin have more clinical experience in these settings.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of dabigatran capsules and Pradaxa oral pellets. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of dabigatran capsules is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Atrial Fibrillation (or Atrial Flutter).** Approve for 1 year if the patient is ≥ 18 years of age.

2. **Deep Vein Thrombosis or Pulmonary Embolism, Treatment.** Approve for 1 year if the patient is ≥ 8 years of age.

3. **Deep Vein Thrombosis or Pulmonary Embolism, To Reduce the Risk of Recurrence.** Approve for 1 year if the patient is ≥ 8 years of age.

4. **Deep Vein Thrombosis or Pulmonary Embolism in a Patient Undergoing Hip Replacement Surgery, Prophylaxis.** Approve for 60 days if the patient is ≥ 18 years of age.

Other Uses with Supportive Evidence

5. **Deep Vein Thrombosis in a Patient Undergoing Knee Replacement Surgery, Prophylaxis.** Approve for 60 days if the patient is ≥ 18 years of age.

6. **Treatment or Prevention of Other Thromboembolic-Related Conditions.** Approve for 6 months if the patient meets both of the following criteria (A and B):
   Note: Examples of other thromboembolic-related conditions include superficial vein thrombosis, splanchnic vein thrombosis, hepatic vein thrombosis, or prophylaxis of venous thromboembolism in a high-risk patient.
   A) Patient is ≥ 8 years of age; AND
   B) Patient meets one of the following (i or ii):
      i. Patient has tried warfarin, fondaparinux, or a low molecular weight heparin product (e.g., enoxaparin, Fragmin [dalteparin injection]); OR
      Note: A patient who has tried Eliquis (apixaban tablets), Xarelto (rivaroxaban tablets), or Savaysa (edoxaban tablets) is not required to try warfarin, fondaparinux, or a low molecular weight heparin product.
      ii. Patient has been started on dabigatran capsules for the treatment of an acute thromboembolic condition.

II. Coverage of Pradaxa oral pellets is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Venous Thromboembolic Events, Treatment.** Approve for 1 year if the patient is ≥ 3 months to < 12 years of age.
   Note: Examples of venous thromboembolic events include deep vein thrombosis, cerebral venous thrombosis or sinus thrombosis, pulmonary embolism, and central-venous thrombosis.

2. **Venous Thromboembolic Events, To Reduce the Risk of Recurrence.** Approve for 1 year if the patient is ≥ 3 months to < 12 years of age.
   Note: Examples of venous thromboembolic events include deep vein thrombosis, cerebral venous thrombosis or sinus thrombosis, pulmonary embolism, and central-venous thrombosis.

Other Uses with Supportive Evidence

3. **Treatment or Prevention of Other Thromboembolic-Related Conditions.** Approve for 6 months if the patient meets both of the following criteria (A and B):
   Note: Examples of other thromboembolic-related conditions include superficial vein thrombosis, splanchnic vein thrombosis, hepatic vein thrombosis, or prophylaxis of venous thromboembolism in a high-risk patient.
   A) Patient is ≥ 3 months to < 12 years of age; AND
   B) Patient meets one of the following (i or ii):
      i. Patient has tried warfarin, fondaparinux, or a low molecular weight heparin product (e.g., enoxaparin, Fragmin [dalteparin injection]); OR
      Note: A patient who has tried Eliquis (apixaban tablets), Xarelto (rivaroxaban tablets and oral suspension), or Savaysa (edoxaban tablets) is not required to try warfarin, fondaparinux, or a low molecular weight heparin product.
      ii. Patient has been started on Pradaxa oral pellets for the treatment of an acute thromboembolic condition.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of dabigatran capsules and Pradaxa oral pellets is not recommended in the following situations:

1. **Venous Thromboembolism in an Acutely Ill Medical Patient, Prophylaxis.** (Note: This includes post-discharge thromboprophylaxis for a patient hospitalized with coronavirus disease 19 [COVID-19]). Xarelto is labeled for prophylaxis of venous thromboembolism in acutely ill medical patients and is supported in clinical practice guidelines, including guidelines which address prophylaxis of venous thromboembolism in COVID-19 patients.[8-11]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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NA – Not applicable.

PRIOR AUTHORIZATION POLICY

POLICY: Anticoagulants – Eliquis Prior Authorization Policy
- Eliquis® (apixaban tablets – Bristol-Myers Squibb/Pfizer)

REVIEW DATE: 01/11/2023

OVERVIEW

Eliquis, a Factor Xa inhibitor, is indicated for the following uses:[1]
- **Non-valvular atrial fibrillation**, to reduce the risk of stroke and systemic embolism.
- **Prophylaxis of deep vein thrombosis (DVT)**, which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.
- **Treatment of DVT and PE**, as well as **reduction in the risk of recurrence of DVT and PE** following initial therapy.

Safety and effectiveness of Eliquis in pediatric patients have not been established.[1]

Guidelines

Guidelines are available which support the use of direct oral anticoagulants (DOACs) in their commonly used clinical settings, such as DVT/PE[2-5] and atrial fibrillation[6,7]. In patients who are eligible for a DOAC, these are generally preferred over vitamin K antagonists (e.g., warfarin). It is noted that in the randomized trials in atrial fibrillation, DOACs were consistently at least non-inferior to warfarin regarding the composite of stroke or systemic embolism and were associated with lower risk of serious bleeding.[7]

Anticoagulants and Coronavirus Disease 19 (COVID-19)

Several clinical practice guidelines have been published with regard to use of anticoagulant therapy in the management of COVID-19. Per National Institutes of Health treatment guidelines regarding antithrombotic therapy in patients with COVID-19 (updated December 28, 2022), hospitalized patients with COVID-19 should not be routinely discharged from the hospital while on venous thromboembolism (VTE) prophylaxis.[8] For patients at low risk for bleeding and high risk for VTE, continuing anticoagulation with an FDA-approved regimen for extended VTE prophylaxis may be considered, as per protocols for patients without COVID-19. Of note, Xarelto® (rivaroxaban tablets and oral suspension) is FDA-approved for prophylaxis of VTE in acutely ill medical patients; Eliquis is not indicated in this setting. Other guidelines have similar recommendations.[9-11]

Other Uses with Supportive Evidence

Although data are not robust regarding use of DOACs in off-label thromboembolic-related conditions, CHEST guidelines (2012) suggest anticoagulation for certain patients with superficial vein thrombosis, symptomatic splanchnic thromboses (portal, mesenteric, and/or splenic vein), or symptomatic hepatic vein thrombosis.[2] The guidelines acknowledge the limited available data in these settings, and all are given Grade 2C recommendations (weak recommendation, low-quality evidence). The 2016 CHEST guideline update did not address these conditions or comment on the role of DOACs.[3] The choice of anticoagulant is often individualized based on patient-specific factors; therefore, for certain patients, DOAC use may be considered in practice. Evidence for DOACs is limited for off-label scenarios; in general, agents such as vitamin K antagonists (e.g., warfarin) and low molecular weight heparin have more clinical experience in these settings.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Eliquis. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Eliquis is recommended in those who meet one of the following criteria:

FDA-Approved Indications

7. **Atrial Fibrillation (or Atrial Flutter).** Approve for 1 year if the patient is ≥ 18 years of age.

8. **Deep Vein Thrombosis in a Patient Undergoing Hip or Knee Replacement Surgery, Prophylaxis.** Approve for 60 days if the patient is ≥ 18 years of age.

9. **Deep Vein Thrombosis or Pulmonary Embolism, Treatment.** Approve for 1 year if the patient is ≥ 18 years of age.

10. **Deep Vein Thrombosis or Pulmonary Embolism to Reduce the Risk of Recurrence.** Approve for 1 year if the patient is ≥ 18 years of age.

Other Uses with Supportive Evidence

11. **Treatment or Prevention of Other Thromboembolic-Related Conditions.** Approve for 6 months if the patient meets both of the following criteria (A and B):
    Note: Examples of other thromboembolic-related conditions include superficial vein thrombosis, splanchnic vein thrombosis, hepatic vein thrombosis, or prophylaxis of venous thromboembolism in a high-risk patient.
    C) Patient is ≥ 18 years of age; AND
    D) Patient meets one of the following (i or ii):
        i. Patient has tried warfarin, fondaparinux injection, or a low molecular weight heparin product (e.g., enoxaparin injection, Fragmin [dalteparin injection]); OR
        Note: A patient who has tried Xarelto (rivaroxaban tablets), Pradaxa (dabigatran capsules), or Savaysa (edoxaban tablets) is not required to try warfarin, fondaparinux, or a low molecular weight heparin product.
        ii. Patient has been started on Eliquis for the treatment of an acute thromboembolic condition.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Eliquis is not recommended in the following situations:

2. **Venous Thromboembolism in an Acutely Ill Medical Patient, Prophylaxis.** (Note: This includes post-discharge thromboprophylaxis for a patient hospitalized with coronavirus disease 19 [COVID-19]). Eliquis has been compared with enoxaparin for post-discharge prophylaxis in acutely ill medical patients; however, superiority vs. enoxaparin was not achieved, and bleeding was increased with Eliquis.[12] Xarelto is labeled for prophylaxis of venous thromboembolism in

acutely ill medical patients and is supported in clinical practice guidelines, including guidelines which address prophylaxis of venous thromboembolism in COVID-19 patients.[8-11]

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Anticoagulants – Savaysa Prior Authorization Policy
- Savaysa® (edoxaban tablets – Daiichi Sankyo)

REVIEW DATE: 01/11/2023

OVERVIEW

Savaysa, a Factor Xa inhibitor, is indicated for the following uses:[1]
- **Non-valvular atrial fibrillation**, to reduce the risk of stroke and systemic embolism.
- **Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)**, following 5 to 10 days of initial therapy with a parenteral anticoagulant.

Savaysa has a unique Boxed Warning regarding reduced efficacy in non-valvular atrial fibrillation in patients with a creatinine clearance > 95 mL/min; Savaysa should be avoided in these individuals.[1] Safety and effectiveness of Savaysa in pediatric patients have not been established.

Guidelines

Guidelines are available which support the use of direct oral anticoagulants (DOACs) in their commonly used clinical settings, such as DVT/PE[2-5] and atrial fibrillation[6,7]. In patients who are eligible for a DOAC, these are generally preferred over vitamin K antagonists (e.g., warfarin). It is noted that in the randomized trials in atrial fibrillation, DOACs were consistently at least non-inferior to warfarin regarding the composite of stroke or systemic embolism and were associated with lower risk of serious bleeding.[7]

Anticoagulants and Coronavirus Disease 19 (COVID-19)

Several clinical practice guidelines have been published with regard to use of anticoagulant therapy in the management of COVID-19. Per National Institutes of Health treatment guidelines regarding antithrombotic therapy in patients with COVID-19 (updated December 28, 2022), hospitalized patients with COVID-19 should not be routinely discharged from the hospital while on venous thromboembolism (VTE) prophylaxis.[8] For patients at low risk for bleeding and high risk for VTE, continuing anticoagulation with an FDA-approved regimen for extended VTE prophylaxis may be considered, as per protocols for patients without COVID-19. Of note, Xarelto® (rivaroxaban tablets and oral suspension) is FDA-approved for prophylaxis of VTE in acutely ill medical patients; Savaysa is not indicated in this setting. Other guidelines have similar recommendations.[9-11]

Other Uses with Supportive Evidence

Savaysa has data for prophylaxis of VTE after hip replacement surgery.[12] Although data are not robust regarding use of DOACs in other off-label thromboembolic-related conditions, CHEST guidelines (2012) suggest anticoagulation for certain patients with superficial vein thrombosis, symptomatic splanchnic thromboses (portal, mesenteric, and/or splenic vein), or symptomatic hepatic vein thrombosis.[2] The guidelines acknowledge the limited available data in these settings, and all are given Grade 2C recommendations (weak recommendation, low-quality evidence). The 2016 CHEST guideline update did not address these conditions or comment on the role of DOACs.[3] The choice of anticoagulant is often individualized based on patient-specific factors; therefore, for certain patients, DOAC use may be considered in practice. Evidence for DOACs is limited for off-label scenarios; in general, agents

such as vitamin K antagonists (e.g., warfarin) and low molecular weight heparin have more clinical experience in these settings.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Savaysa. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Savaysa is recommended in those who meet one of the following criteria:

FDA-Approved Indications

12. **Atrial Fibrillation (or Atrial Flutter).** Approve for 1 year if the patient meets both of the following criteria (A and B):
    A) Patient is ≥ 18 years of age; AND
    B) Patient has an estimated creatinine clearance ≤ 95 mL/min.

13. **Deep Vein Thrombosis or Pulmonary Embolism, Treatment.** Approve for 1 year if the patient is ≥ 18 years of age.

Other Uses with Supportive Evidence

14. **Deep Vein Thrombosis in a Patient Undergoing Hip Replacement Surgery, Prophylaxis.** Approve for 60 days if the patient is ≥ 18 years of age.

15. **Treatment or Prevention of Other Thromboembolic-Related Conditions.** Approve for 6 months if the patient meets both of the following criteria (A and B):
    Note: Examples of other thromboembolic-related conditions include superficial vein thrombosis, splanchnic vein thrombosis, hepatic vein thrombosis, or prophylaxis of venous thromboembolism in a high-risk patient.
    E) Patient is ≥ 18 years of age; AND
    F) Patient meets one of the following criteria (i or ii):
        i. Patient has tried warfarin, fondaparinux, or a low molecular weight heparin product (e.g., enoxaparin, Fragmin [dalteparin injection]); OR
        Note: A patient who has tried Eliquis (apixaban tablets), Xarelto (rivaroxaban tablets), or Pradaxa (dabigatran capsules) is not required to try warfarin, fondaparinux, or a low molecular weight heparin.
        ii. Patient has been started on Savaysa for the treatment of an acute thromboembolic condition.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Savaysa is not recommended in the following situations:

3. **Venous Thromboembolism in an Acutely Ill Medical Patient, Prophylaxis.** (Note: This includes post-discharge thromboprophylaxis for a patient hospitalized with coronavirus disease 19 [COVID-19]). Xarelto is labeled for prophylaxis of venous thromboembolism in acutely ill medical patients and is supported in clinical practice guidelines, including guidelines which address prophylaxis of venous thromboembolism in COVID-19 patients.[7-9]

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Anticoagulants – Xarelto Prior Authorization Policy
- Xarelto® (rivaroxaban tablets and oral suspension – Janssen)

REVIEW DATE: 01/11/2023

OVERVIEW

Xarelto, an oral Factor Xa inhibitor, is indicated for the following uses:[1]

- **Atrial fibrillation**, non-valvular, to reduce the risk of stroke and systemic embolism in adults.
- **Coronary artery disease**, in combination with aspirin, to reduce the risk of major adverse cardiovascular events in adults.
- **Prophylaxis of deep vein thrombosis (DVT),** which may lead to pulmonary embolism (PE), in patients undergoing knee or hip replacement surgery in adults.
- **Prophylaxis of venous thromboembolism in acutely ill medical patients**, in adults at risk for thromboembolic complications not at high risk of bleeding.
- **Peripheral artery disease**, in adults, including patients after recent lower extremity revascularization due to symptomatic peripheral artery disease, in combination with aspirin to reduce the risk of major thrombotic vascular events.
- **Treatment of DVT** and **PE**, as well as **reduction in the risk of recurrence of DVT and/or PE** in patients at continued risk for recurrent DVT and/or PE after completion of initial treatment. These indications includes patients birth to < 18 years of age as well as adults.
- **Thromboprophylaxis in a patient with congenital heart disease after the Fontan procedure**, in pediatric patients ≥ 2 years of age.

Dosing and Administration

In the prescribing information for Xarelto tablets and oral suspension, it is noted that for adults who are unable to swallow whole tablets, Xarelto tablets (all strengths) may be crushed and mixed with applesauce immediately prior to use and administered orally.[1] Xarelto tablets (all strengths) may be crushed and suspended in water for administration via nasogastric or gastric tube. Xarelto oral suspension may also be given through nasogastric or gastric tube.

For pediatric patients, tablets must not be split in an attempt to provide a fraction of a tablet dose. For treatment of venous thromboembolism (VTE) and reduction in risk of VTE recurrence in pediatric patients, it is noted that oral suspension or tablets may be used for a patient weighing ≥ 30 kg; for patients weighing < 30 kg, oral suspension should be used. For thromboprophylaxis in pediatric patients with congenital heart disease after the Fontan procedure, oral suspension or tablets may be used for a patient weighing ≥ 50 kg; oral suspension is needed for a patient weighing < 50 kg. It is noted that there are no safety, efficacy, pharmacokinetic, and pharmacodynamic data to support the use of Xarelto 2.5 mg tablets in pediatric patients; therefore, Xarelto 2.5 mg tablets are not recommended in pediatric patients.

Guidelines

Guidelines are available which support the use of direct oral anticoagulants (DOACs) in their commonly used clinical settings, such as DVT/PE[2-5] and atrial fibrillation[6,7]. In patients who are eligible for a DOAC, these are generally preferred over vitamin K antagonists (e.g., warfarin). It is noted that in the randomized trials in atrial fibrillation, DOACs were consistently at least non-inferior to warfarin regarding the composite of stroke or systemic embolism and were associated with lower risk of serious bleeding.[7]

Anticoagulants and Coronavirus Disease 19 (COVID-19)

Several clinical practice guidelines have been published with regard to use of anticoagulant therapy in the management of COVID-19. Per National Institutes of Health treatment guidelines regarding antithrombotic therapy in patients with COVID-19 (updated December 28, 2022), hospitalized patients with COVID-19 should not be routinely discharged from the hospital while on VTE prophylaxis.[8] For patients at low risk for bleeding and high risk for VTE, continuing anticoagulation with an FDA-approved regimen for extended VTE prophylaxis may be considered, as per protocols for patients without COVID-19. Of note, Xarelto is FDA-approved for prophylaxis of VTE in acutely ill medical patients. Other guidelines have similar recommendations.[9-11]

Other Uses with Supportive Evidence

Although data are not robust regarding use of DOACs in off-label thromboembolic-related conditions, CHEST guidelines (2012) suggest anticoagulation for certain patients with superficial vein thrombosis, symptomatic splanchnic thromboses (portal, mesenteric, and/or splenic vein), or symptomatic hepatic vein thrombosis.[2] The guidelines acknowledge the limited available data in these settings, and all are given Grade 2C recommendations (weak recommendation, low-quality evidence). The 2016 CHEST guideline update did not address these conditions or comment on the role of DOACs.[3] The choice of anticoagulant is often individualized based on patient-specific factors; therefore, for certain patients, DOAC use may be considered in practice. Evidence for DOACs is limited for off-label scenarios; in general, agents such as vitamin K antagonists (e.g., warfarin) and low molecular weight heparin have more clinical experience in these settings.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Xarelto. All approvals are provided for the approval duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xarelto (tablets and oral suspension) is recommended in those who meet one of the following criteria:

FDA-Approved Indications

- **Atrial Fibrillation (or Atrial Flutter).** Approve for 1 year if the patient meets both of the following criteria (A and B):
    - Patient is ≥ 18 years of age; AND
    - If Xarelto oral suspension is being requested, approve if the patient is unable to have Xarelto tablets appropriately administered.

2. **Coronary Artery Disease**. Approve for 1 year if the patient meets all of the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient will be taking concomitant aspirin at least 75 mg daily; AND
    - If Xarelto oral suspension is being requested, approve if the patient is unable to have Xarelto tablets appropriately administered.

3. **Deep Vein Thrombosis in a Patient Undergoing Knee or Hip Replacement Surgery, Prophylaxis.** Approve for 60 days if the patient meets both of the following (A and B):

A) Patient is ≥ 18 years of age; AND
B) If Xarelto oral suspension is being requested, approve if the patient is unable to have Xarelto tablets appropriately administered.

4. **Deep Vein Thrombosis or Pulmonary Embolism, Treatment.** Approve for 1 year if the patient meets one of the following (A or B):
   A) Xarelto tablets: Approve.
   B) Xarelto oral suspension: Approve if the patient meets one of the following (i or ii):
      i. Patient is unable to have Xarelto tablets appropriately administered; OR
      ii. The prescribed Xarelto dose cannot be achieved by Xarelto 10 mg, 15 mg, or 20 mg tablets.

5. **Deep Vein Thrombosis or Pulmonary Embolism, to Reduce the Risk of Recurrence.** Approve for 1 year if the patient meets one of the following (A or B):
   A) Xarelto tablets: Approve.
   B) Xarelto oral suspension: Approve if the patient meets one of the following (i or ii):
      i. Patient is unable to have Xarelto tablets appropriately administered; OR
      ii. The prescribed Xarelto dose cannot be achieved by Xarelto 10 mg, 15 mg, or 20 mg tablets.

6. **Peripheral Artery Disease**. Approve for 1 year if the patient meets all of the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient will be taking concomitant aspirin at least 75 mg daily; AND
   C) If Xarelto oral suspension is being requested, patient is unable to have Xarelto tablets appropriately administered.

7. **Thromboprophylaxis in a Patient with Congenital Heart Disease**. Approve for 1 year if the patient meets both of the following (A, B, and C):
   A) Patient is ≥ 2 years of age and < 18 years of age; AND
   B) Patient has undergone the Fontan procedure; AND
   C) If Xarelto oral suspension is being requested, patient meets one of the following (i or ii):
      i. Patient is unable to have Xarelto tablets appropriately administered; OR
      ii. The prescribed Xarelto dose cannot be achieved by Xarelto 10 mg, 15 mg, or 20 mg tablets.

8. **Venous Thromboembolism in an Acutely Ill Medical Patient, Prophylaxis.** Approve for 60 days if the patient meets both of the following (A and B):
   Note: This includes post-discharge thromboprophylaxis for a patient hospitalized with coronavirus disease 19 (COVID-19).
   A) Patient is ≥ 18 years of age; AND
   B) If Xarelto oral suspension is being requested, patient is unable to have Xarelto tablets appropriately administered.

Other Uses with Supportive Evidence

9. **Treatment or Prevention of Other Thromboembolic-Related Conditions.** Approve for 6 months if the patient meets both of the following criteria (A and B):
   Note: Examples of other thromboembolic-related conditions include superficial vein thrombosis, splanchnic vein thrombosis, hepatic vein thrombosis, or prophylaxis of venous thromboembolism in a high-risk patient.
   A) Patient meets one of the following (i or ii):
      i. Patient has tried warfarin, fondaparinux or a low molecular weight heparin product (e.g., enoxaparin, Fragmin [dalteparin injection]); OR

Note: A patient who has tried Eliquis (apixaban tablets), Pradaxa (dabigatran capsules), or Savaysa (edoxaban tablets) is not required to try warfarin, fondaparinux, or a low molecular weight heparin.

ii. Patient has been started on Xarelto for the treatment of an acute thromboembolic condition; AND

B) If Xarelto oral suspension is being requested, approve if the patient meets one of the following (i or ii):

i. Patient unable to have Xarelto tablets appropriately administered; OR

ii. The prescribed Xarelto dose cannot be achieved by Xarelto 10 mg, 15 mg, or 20 mg tablets.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xarelto is not recommended in the following situations:

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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54. Guyatt GH, Akl EA, Crowther M, et al, for the American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:7S-47S.
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NA – Not applicable.

PRIOR AUTHORIZATION POLICY

POLICY: Antifungals (Azoles) – Intravenous Products Prior Authorization Policy
- Cresemba® (isavuconazonium sulfate intravenous infusion – Astellas)
- Fluconazole intravenous infusion – generic only
- Noxafil® (posaconazole intravenous infusion – Merck)
- Vfend® (voriconazole intravenous infusion – Pfizer, generic)

REVIEW DATE: 03/01/2023

OVERVIEW

Cresemba intravenous infusion, fluconazole intravenous infusion, Noxafil intravenous infusion, and voriconazole intravenous infusion are azole antifungals. These products are indicated for prophylaxis and/or treatment of **systemic fungal infections**, including *Candida* infections, cryptococcal meningitis, esophageal candidiasis, invasive aspergillosis, and invasive mucormycosis.[1-4] The specific indications are different for the four products; refer to the prescribing information for details.

Injectable formulations of some antifungals have been compounded with other topical products (clindamycin, clotrimazole, ketoconazole, and mupirocin) to make foot baths and other products. There are no data to support these uses.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of the intravenous formulations of Cresemba, fluconazole, Noxafil, and voriconazole when these products are prescribed in conjunction with select topical products: clindamycin, clotrimazole, ketoconazole, and mupirocin. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: If there are no prescription claims for topical clindamycin, topical clotrimazole, topical ketoconazole, and/or topical mupirocin products in the past 180 days, the Prior Authorization edit will not be applied in adjudication. Prior Authorization will only apply to prescriptions for the intravenous formulations of Cresemba, fluconazole, Noxafil, and voriconazole when there is of topical clindamycin, topical clotrimazole, topical ketoconazole, and/or topical mupirocin products in the past 180 days.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cresemba, fluconazole, Noxafil, and voriconazole is recommended in those who meet the following criteria:

FDA-Approved Indication

4. Systemic Fungal Infections (Prophylaxis or Treatment). Approve for 3 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cresemba, fluconazole, Noxafil, and voriconazole is not recommended in the following situations:

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

3. Cresemba® capsule and intravenous infusion [prescribing information]. Northbrook, IL: Astellas; November 2022.
4. Fluconazole intravenous infusion [prescribing information]. Schaumburg, IL: Sagent Pharmaceuticals; November 2020.
5. Noxafil® intravenous infusion, delayed-release tablets, oral suspension [prescribing information]. Whitehouse Station, NJ: Merck; September 2022.
6. Vfend® intravenous infusion [prescribing information]. New York, NY: Pfizer; October 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Antifungals – Cresemba (Oral) Prior Authorization Policy
- Cresemba® (isavuconazonium sulfate capsules – Astellas Pharma)

REVIEW DATE: 07/26/2023

OVERVIEW

Cresemba, an azole antifungal, is indicated in adults for the following uses:[1]
- **Invasive aspergillosis.**
- **Invasive mucormycosis.**

Cresemba is also available for use as an intravenous (IV) infusion.[1] Switching between the IV and oral formulation is acceptable as the two formulations are bioequivalent. Patients are typically transitioned from the IV formulation to the oral formulation while in the hospital or upon discharge. In the pivotal study involving patients with invasive aspergillosis, patients were initiated on IV Cresemba before transitioning to oral Cresemba therapy. The mean treatment duration was 47 days, of which patients received IV Cresemba for 8 to 9 days. In an open-label, non-comparative study that included a subset of patients with invasive mucormycosis, patients were treated with either IV or oral Cresemba. The median duration of Cresemba therapy was 102 days for patients classified as primary, 33 days for refractory, and 85 days for intolerant.

Guidelines/Recommendations

The Infectious Diseases Society of America (IDSA) [2016] recommends Cresemba as a treatment option for invasive aspergillosis and different invasive syndromes of *Aspergillus* (e.g., invasive pulmonary aspergillosis, invasive sinus aspergillosis, aspergillosis of the central nervous system).[2] Treatment of invasive aspergillosis should be continued for a minimum of 6 to 12 weeks, depending on the degree and duration of immunosuppression, site of disease, and evidence of disease improvement.

Other Uses with Supportive Evidence

The National Comprehensive Cancer Network (NCCN) Prevention and Treatment of Cancer-Related Infections (version 1.2023 – June 28, 2023) notes that use of Cresemba may be considered for patients who have invasive or refractory aspergillosis or mucormycosis or who have intolerance to amphotericin B formulations.[3] NCCN also notes Cresemba as a treatment option for the prevention of fungal infections in patients with significant graft-versus-host disease (GVHD) [especially grade 3/4] who are receiving immunosuppressive therapy; treatment should continue until resolution of significant GVHD. Cresemba is also a treatment option for these groups of patients with neutropenia: patients with myelodysplastic syndrome, patients with acute myeloid leukemia, and patients who are allogeneic hematopoietic cell transplant recipients; treatment should continue until resolution of neutropenia.

The guidelines for prevention and treatment of opportunistic infections in adults and adolescents with human immunodeficiency virus (HIV) infections (last updated June 2023) note Cresemba as a treatment option for patients with HIV and esophageal candidiasis.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cresemba capsules. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cresemba capsules is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. ***Aspergillus* Infection – Treatment.** Approve for 3 months.

2. **Mucormycosis – Treatment.** Approve for 3 months.

Other Uses with Supportive Evidence

3. **Candidiasis (Systemic) in a Patient with Human Immunodeficiency Virus (HIV) Infection – Treatment.** Approve for 3 months.

4. **Fungal Infection (Systemic) in a Patient With Cancer and Neutropenia – Prophylaxis.** Approve for 6 months.
   Note: Examples of cancers predisposing neutropenic patients to risk of fungal infections include: myelodysplastic syndrome, acute myeloid leukemia, patients post-allogeneic hematopoietic cell transplant.

5. **Fungal Infection (Systemic) in a Patient with Graft-versus-Host Disease – Prophylaxis**. Approve for 6 months.

6. **Fungal Infection (Systemic) That Is Susceptible to Cresemba – Treatment.** Approve for 3 months.

7. **Patient is Currently Receiving Cresemba.** Approve for 3 months to complete the course of therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cresemba capsules is not recommended in the following situations:

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

7. Cresemba® capsules [prescribing information]. Northbrook, IL: Astellas Pharma; November 2022.
8. Patterson TF, Thompson GR, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;63(4):e1-e60.
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10. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and

Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-oi/guidelines-adult-adolescent-oi.pdf. Last updated June 14, 2023. Accessed on July 13, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Antifungals – Flucytosine Prior Authorization Policy
- Ancobon® (flucytosine capsules – Bausch Health, generic)

REVIEW DATE: 05/03/2023

OVERVIEW

Flucytosine, an antifungal, is indicated for the treatment of serious infections caused by susceptible strains of *Candida* and/or *Cryptococcus*:[1]

- ***Candida* infections:** Septicemia, endocarditis, and urinary system infections have been effectively treated with flucytosine. Limited trials in pulmonary infections justify the use of flucytosine.
- ***Cryptococcus* infections:** Meningitis and pulmonary infections have been treated effectively. Studies in septicemias and urinary tract infections are limited, but good responses have been reported.

Flucytosine should be used in combination with amphotericin B for the treatment of systemic candidiasis and cryptococcosis due to emergence of resistance to flucytosine.

Treatment duration is varied; patients are treated until infection has cleared.[2-4]

There have been reports of flucytosine capsules being compounded for use as foot baths. There are no data to support the use of flucytosine capsules in this manner and coverage of flucytosine capsules for this use is not recommended.

Guidelines/Recommendations

Infectious Diseases Society of America (IDSA) guidelines for treatment of *Candida* infections (2016) and *Cryptococcus* infections (2010) are available and guidelines address use of flucytosine for these infections.[2,3] Guidelines note that flucytosine can be used as monotherapy or in combination with other antifungals for these infections.

Flucytosine capsules may be extemporaneously compounded for vaginal use for patients with vulvovaginal candidiasis.[2,4] IDSA guidelines for the management of candidiasis (2016) note 17% flucytosine cream to be an option, as monotherapy or in combination with 3% amphotericin B cream, for the treatment of *C. glabrata* vulvovaginitis unresponsive to oral azole antifungals (weak recommendation; low quality evidence); duration of treatment is 14 days.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of flucytosine capsules. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of flucytosine capsules is recommended in those who meet one of the following criteria:

FDA-Approved Indications

8. ***Candida* Infection (Systemic) – Treatment.** Approve for 3 months.

9. ***Cryptococcus* Infection (Systemic) – Treatment.** Approve for 3 months.

Other Uses with Supportive Evidence

10. **Fungal Infection (Systemic) That Is Susceptible to Flucytosine – Treatment.** Approve for 3 months.

11. **Vulvovaginal candidiasis.** Approve for 14 days if the patient has previously tried at least one other antifungal therapy.

12. **Patient is Currently Receiving Flucytosine For a Systemic Fungal Infection.** Approve for 3 months to complete the course of therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of flucytosine capsules is not recommended in the following situations:

7. **Foot baths.** There are no data to support the use of flucytosine capsules for use as foot baths.

8. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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14. Facts and Comparisons® Online. Wolters Kluwer Health, Inc.; 2023. Available at: https://fco.factsandcomparisons.com/lco/action/home. Accessed on April 26, 2023. Search term: flucytosine.

PRIOR AUTHORIZATION POLICY

POLICY: Antifungals – Posaconazole (Oral) Prior Authorization Policy
- Noxafil® (posaconazole delayed-release tablets [generic], oral suspension [generic], PowderMix for delayed-release oral suspension – Merck)

REVIEW DATE: 07/26/2023

OVERVIEW

Posaconazole, an azole antifungal, is indicated for the following uses:[1]

- **Prophylaxis of invasive *Aspergillus* and *Candida* infections** in patients who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy: delayed-release tablets, in patients ≥ 2 years of age who weigh > 40 kg; oral suspension, in patients ≥ 13 years of age; Noxafil PowderMix for delayed-release oral suspension, in pediatric patients ≥ 2 years of age who weigh < 40 kg.
- **Treatment of invasive aspergillosis** in patients ≥ 13 years of age (delayed-release tablets).
- **Treatment of oropharyngeal candidiasis** including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole, in patients ≥ 13 years of age (oral suspension).

The duration of posaconazole therapy is varied. In a pivotal study, where posaconazole oral suspension was compared with fluconazole capsules as prophylaxis for the prevention of invasive fungal infections in allogeneic HSCT recipients with GVHD, the mean duration of posaconazole therapy was 80 days.[1]

Guidelines

The Infectious Diseases Society of America (IDSA) guidelines for aspergillosis (2016) recommend posaconazole for treatment and prophylaxis of invasive aspergillosis.[2] The IDSA guidelines for candidiasis (2016) and the National Comprehensive Cancer Network (NCCN) Guidelines for the Prevention and Treatment of Cancer-Related Infections (version 1.2023 – June 28, 2023) note posaconazole as one of the drugs of choice for the treatment of fluconazole-refractory oropharyngeal candidiasis.[3,5] The IDSA notes posaconazole as having high-quality evidence for prophylaxis of candidiasis.

NCCN notes posaconazole is active against *Candida* and *Aspergillus* species, some *Mucorales spp*, some of the rarer molds, and against dimorphic fungi. Posaconazole is noted as a treatment option for the prevention of fungal infections in patients with significant graft-versus-host disease (GVHD) [especially grade 3/4] who are receiving immunosuppressive therapy; treatment should continue until resolution of significant GVHD. Posaconazole is also a treatment option for these groups of patients with neutropenia: patients with myelodysplastic syndrome, patients with acute myeloid leukemia, and patients who are allogeneic hematopoietic cell transplant recipients; treatment should continue until resolution of neutropenia. NCCN also notes posaconazole as a treatment option for the treatment of the following infections: mouth and esophageal infections (e.g., oral thrush) refractory to fluconazole; invasive fusariosis; *Scedosporium* infections; and maintenance treatment of mucormycosis.[5] In addition, posaconazole is a treatment option for patients with invasive, refractory infections who have intolerance to amphotericin B formulations.

The guidelines for prevention and treatment of opportunistic infections in adults and adolescents with human immunodeficiency virus (HIV) infections (last updated June 2023) note posaconazole as an option for treatment of patients with coccidioidomycosis, or histoplasmosis; and as chronic suppressive treatment of esophageal candidiasis.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Noxafil/posaconazole (oral). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Noxafil/posaconazole is recommended in those who meet one of the following criteria:

FDA-Approved Indications

13. ***Aspergillus* Infection – Prophylaxis.** Approve for 6 months.

14. ***Aspergillus* Infection – Treatment.** Approve for 3 months.

15. ***Candida* Infection (Systemic) – Prophylaxis.** Approve for 6 months.

16. **Oropharyngeal Candidiasis – Treatment.** Approve for 3 months.

Other Uses with Supportive Evidence

17. **Esophageal Candidiasis in a Patient with Human Immunodeficiency Virus (HIV) Infection – Chronic Suppressive Treatment**. Approve for 6 months.

18. **Fungal Infection (Systemic) in a Patient With Cancer and Neutropenia – Prophylaxis.** Approve for 6 months.
    Note: Examples of cancers predisposing neutropenic patients to risk of fungal infections include: myelodysplastic syndrome, acute myeloid leukemia, patients post-allogeneic hematopoietic cell transplant.

19. **Fungal Infection (Systemic) in a Patient with Graft-versus-Host Disease - Prophylaxis**. Approve for 6 months.

20. **Fungal Infection (Systemic) in a Patient with Human Immunodeficiency Virus (HIV) Infection – Treatment.** Approve for 3 months.

21. **Fusariosis, Invasive – Treatment.** Approve for 3 months.

22. **Mouth and Esophageal Infection (Refractory to Other Azole Antifungals) – Treatment.** Approve for 3 months.

23. **Mucormycosis – Maintenance Treatment.** Approve for 6 months.

24. ***Scedosporium*** **Infection – Treatment.** Approve for 3 months.

25. Fungal Infection (Systemic) that is Susceptible to Posaconazole – Treatment. Approve for 3 months.

26. Patient is Currently Receiving Posaconazole. Approve for 3 months to complete the course of therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Noxafil/Posaconazole (oral) is not recommended in the following situations:

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

15. Noxafil® intravenous infusion, delayed-release tablets, oral suspension, and delayed-release oral suspension [prescribing information]. Whitehouse Station, NJ: Merck; January 2022.
16. Patterson TF, Thompson GR, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2016;63(4):e1-e60.
17. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guidelines for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2016;62(4):e1-50.
18. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-oi/guidelines-adult-adolescent-oi.pdf. . Last updated June 14, 2023. Accessed on July 14, 2023.
19. The NCCN Prevention and Treatment of Cancer-Related Infections Clinical Practice Guidelines in Oncology (version 1.2023 – June 28, 2023). ©2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 14, 2023.

PRIOR AUTHORIZATION WITH STEP THERAPY POLICY

POLICY: Antifungals – Tolsura Prior Authorization with Step Therapy Policy
- Tolsura® (itraconazole capsules – Mayne Pharma)

REVIEW DATE: 07/26/2023

OVERVIEW

Tolsura, an azole antifungal, is indicated in immunocompromised and non-immunocompromised adults for the following uses:[1]

- **Aspergillosis**, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy.
- **Blastomycosis**, pulmonary and extrapulmonary.
- **Histoplasmosis**, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis.

Limitation of use: Tolsura is not indicated for the treatment of onychomycosis. Tolsura is not interchangeable or substitutable with other itraconazole products due to the differences in the dosing between Tolsura and other itraconazole products.

Tolsura contains itraconazole dispersed in a polymer matrix and encapsulated in a hard gelatin capsule.[1] Compared with conventional itraconazole, Tolsura has improved overall absorption.[2] Itraconazole capsules (Sporanox®, generic) are also indicated for these uses; itraconazole capsules are also indicated for the treatment of onychomycosis in non-immunocompromised patients.[3] Itraconazole oral solution (Sporanox®, generic) is indicated for the treatment of oropharyngeal and esophageal candidiasis.[4] The drug exposure with itraconazole oral solution is greater than that of the capsules when the same dose of drug is given.

Guidelines

The use of Tolsura in the prevention/treatment of systemic fungal infections is not addressed in guidelines.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tolsura. This Prior Authorization Policy also contains a Step Therapy component. When clinically appropriate, patients are directed to try one Step 1 Product (itraconazole capsules or oral solution) prior to Tolsura (Step 2). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tolsura is recommended in those who meet one of the following criteria:

FDA-Approved Indications

5. **Aspergillosis – Pulmonary or Extrapulmonary – Treatment.** Approve for 3 months if the patient meets one of the following (A or B):
   - **a)** Patient has tried one of itraconazole capsules or oral solution; OR
   - **b)** Patient is currently receiving Tolsura for this condition.

6. **Blastomycosis – Pulmonary or Extrapulmonary – Treatment.** Approve for 3 months if the patient meets one of the following (A or B):
   - **a)** Patient has tried one of itraconazole capsules or oral solution; OR
   - **b)** Patient is currently receiving Tolsura for this condition.

7. **Histoplasmosis – Including Chronic Cavitary Pulmonary Disease and Disseminated, Non-Meningeal – Treatment.** Approve for 3 months if the patient meets one of the following (A or B):
   - **a)** Patient has tried one of itraconazole capsules or oral solution; OR
   - **b)** Patient is currently receiving Tolsura for this condition.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tolsura is not recommended in the following situations:

10. **Onychomycosis.** Tolsura is not indicated for the treatment of onychomycosis (noted as a Limitation of Use in the Tolsura prescribing information).[1]

11. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

20. Tolsura® capsule [prescribing information]. Greenville, SC: Mayne Pharma; December 2018.
21. Tolsura – Advanced antifungal delivery technology. Available at: https://tolsura.com/about-tolsura/. Accessed on July 14, 2023.
22. Sporanox® capsule [prescribing information]. Titusville, NJ: Janssen; December 2019.
23. Sporanox® oral solution [prescribing information]. Titusville, NJ: Janssen; April 2019.

PRIOR AUTHORIZATION POLICY

POLICY: Antifungals – Vivjoa Prior Authorization Policy
- Vivjoa™ (oteseconazole capsules – Mycovia)

REVIEW DATE: 08/23/2023

OVERVIEW

Vivjoa, an azole antifungal, is indicated to reduce the incidence of **recurrent vulvovaginal candidiasis** (RVVC) in females with a of RVVC who are not of reproductive potential.[1] Females who are NOT of reproductive potential are defined as: persons who are biological females who are postmenopausal or have another reason for permanent infertility (e.g., tubal ligation, hysterectomy, salpingo-oophorectomy). Vivjoa is contraindicated in females of reproductive potential and in pregnant and lactating women.

The Vivjoa pivotal studies enrolled females with RVVC, which was defined as three or more episodes of vulvovaginal candidiasis in a 12-month period; this definition aligns with the Centers for Disease Control and Prevention's (CDC) definition of RVVC.[1,2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vivjoa. All approvals are provided for 30 days, which is an adequate duration for the patient to receive one course of treatment.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vivjoa is recommended in those who meet the following criteria:

FDA-Approved Indication

6. Recurrent Vulvovaginal Candidiasis. Approve one course of treatment if the patient meets ALL of the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has had at least three episodes of vulvovaginal candidiasis in a 12-month period; AND
  Note: A patient who has had two or more previous episodes of vulvovaginal candidiasis in the previous 12 months (prior to the current infection) would meet this requirement.
- **C)** Patient is NOT of reproductive potential; AND
  Note: A person who is NOT of reproductive potential is defined as a person who is a biological female who is postmenopausal or has another reason for permanent infertility (e.g., tubal ligation, hysterectomy, salpingo-oophorectomy).
- **D)** Patient is NOT pregnant; AND
- **E)** Patient is NOT breastfeeding.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vivjoa is not recommended in the following situations:

12. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

64. Vivjoa™ capsules [prescribing information]. Durham, NC: Mycovia; April 2022.
65. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines 2021. *MMWR Recomm Rep*. 2021;70(4):1-187.

PRIOR AUTHORIZATION POLICY

POLICY: Antifungals – Voriconazole (Oral) Prior Authorization with Step Therapy Policy
- Vfend® (voriconazole tablets and oral suspension – Roerig/Pfizer, generic)

REVIEW DATE: 07/26/2023

OVERVIEW

Voriconazole, an azole antifungal, is indicated in patients ≥ 2 years of age for the following uses:[1]
- **Candidemia,** in non-neutropenic patients and other deep tissue *Candida* infections.
- **Esophageal candidiasis.**
- **Invasive aspergillosis.**
- ***Scedosporium apiospermum*** (asexual form of *Pseudallescheria boydii*) and ***Fusarium spp***. (including *Fusarium solani*), in patients intolerant of, or refractory to, other therapy.

The duration of voriconazole therapy is varied, ranging from a median duration of 15 days for esophageal candidiasis to 76 days for invasive aspergillosis.[1]

Guidelines

The Infectious Diseases Society of America (IDSA) recommends voriconazole as a treatment option for the treatment or prevention of invasive aspergillosis (2016) and for candidemia and candidiasis.[2,3] Use of voriconazole for treatment of infections caused by *Candida* spp and *Aspergillus* spp are also noted in the National Comprehensive Cancer Network (NCCN) guidelines for the prevention and treatment of cancer-related infections (version 1.2023 – June 28, 2023).[4] The IDSA guidelines for management of candidiasis note voriconazole has demonstrated effectiveness for candidemia and candidiasis, including mucosal and invasive candidiasis (e.g., *Candida* intravascular infections, including endocarditis and infections of implantable cardiac devices; fluconazole-refractory oropharyngeal candidiasis; *Candida* endophthalmitis).[3] Voriconazole represents an option in the first-line treatment of infections due to *Scedosporium* spp and *Fusarium* spp.[5]

NCCN also notes voriconazole as a treatment option for the prevention of fungal infections in patients with significant graft-versus-host disease (GVHD) [especially grade 3/4] who are receiving immunosuppressive therapy; treatment should continue until resolution of significant GVHD.[4] Voriconazole is also a treatment option for these groups of patients with neutropenia: patients with myelodysplastic syndrome, patients with acute myeloid leukemia, and patients who are allogeneic hematopoietic cell transplant recipients; treatment should continue until resolution of neutropenia.

The IDSA guidelines for the management of blastomycosis (2008) note voriconazole as an option for the treatment of central nervous system blastomycosis.[6]

The Guidelines for Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with Human Immunodeficiency Virus (HIV) Infections (last updated June 2023) recommend voriconazole as a treatment option for the prophylaxis/treatment of various fungal infections (e.g., histoplasmosis, coccidioidomycosis, and talaromycosis) in patients with HIV.[7]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Vfend tablets and oral suspension and generic voriconazole tablets and oral suspension. This Prior Authorization Policy also contains a Step Therapy component. When clinically appropriate, patients are directed to try the generic product. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Vfend/Voriconazole is recommended in those who meet one of the following criteria:

FDA-Approved Indications

27. *Aspergillus* Infection – Treatment. Approve for 3 months if the patient meets one of the following (A or B):
A) Generic voriconazole tablets or oral suspension is requested; OR
B) Patient meets both of the following (i and ii):
   i. Patient has tried the corresponding generic voriconazole product (tablet or oral suspension); AND
   ii. Patient cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescriber, would result in a significant allergy or serious adverse reaction.

28. *Candida* (Systemic) Infection – Treatment. Approve for 3 months if the patient meets one of the following (A or B):
A) Generic voriconazole tablets or oral suspension is requested; OR
B) Patient meets both of the following (i and ii):
   i. Patient has tried the corresponding generic voriconazole product (tablet or oral suspension); AND
   ii. Patient cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescriber, would result in a significant allergy or serious adverse reaction.

29. Esophageal Candidiasis – Treatment. Approve for 3 months if the patient meets one of the following (A or B):
A) Generic voriconazole tablets or oral suspension is requested; OR
B) Patient meets both of the following (i and ii):
   i. Patient has tried the corresponding generic voriconazole product (tablet or oral suspension); AND
   ii. Patient cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescriber, would result in a significant allergy or serious adverse reaction.

30. ***Fusarium*** **Infection – Treatment.** Approve for 3 months if the patient meets one of the following (A or B):

A) Generic voriconazole tablets or oral suspension is requested; OR

B) Patient meets both of the following (i and ii):

i. Patient has tried the corresponding generic voriconazole product (tablet or oral suspension); AND

ii. Patient cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescriber, would result in a significant allergy or serious adverse reaction.

31. ***Scedosporium apiospermum*** **Infection – Treatment.** Approve for 3 months if the patient meets one of the following (A or B):

A) Generic voriconazole tablets or oral suspension is requested; OR

B) Patient meets both of the following (i and ii):

i. Patient has tried the corresponding generic voriconazole product (tablet or oral suspension); AND

ii. Patient cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescriber, would result in a significant allergy or serious adverse reaction.

Other Uses with Supportive Evidence

32. ***Aspergillus*** **Infection – Prophylaxis.** Approve for 6 months if the patient meets one of the following (A or B):

A) Generic voriconazole tablets or oral suspension is requested; OR

B) Patient meets both of the following (i and ii):

i. Patient has tried the corresponding generic voriconazole product (tablet or oral suspension); AND

ii. Patient cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescriber, would result in a significant allergy or serious adverse reaction.

33. Blastomycosis – Treatment. Approve for 3 months if the patient meets one of the following (A or B):

A) Generic voriconazole tablets or oral suspension is requested; OR

B) Patient meets both of the following (i and ii):

i. Patient has tried the corresponding generic voriconazole product (tablet or oral suspension); AND

ii. Patient cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescriber, would result in a significant allergy or serious adverse reaction.

34. ***Candida*** **Endophthalmitis – Treatment.** Approve for 3 months if the patient meets one of the following (A or B):

A) Generic voriconazole tablets or oral suspension is requested; OR

B) Patient meets both of the following (i and ii):

i. Patient has tried the corresponding generic voriconazole product (tablet or oral suspension); AND

ii. Patient cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescriber, would result in a significant allergy or serious adverse reaction.

35. Fungal Infection (Systemic) in a Patient With Cancer and Neutropenia – Prophylaxis. Approve for 6 months if the patient meets one of the following (A or B):
Note: Examples of cancers predisposing neutropenic patients to risk of fungal infections include: myelodysplastic syndrome, acute myeloid leukemia, patients post-allogeneic hematopoietic cell transplant

A) Generic voriconazole tablets or oral suspension is requested; OR

B) Patient meets both of the following (i and ii):

i. Patient has tried the corresponding generic voriconazole product (tablet or oral suspension); AND

ii. Patient cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescriber, would result in a significant allergy or serious adverse reaction.

10. Fungal Infection (Systemic) in a Patient with Graft-versus-Host Disease - Prophylaxis. Approve for 6 months if the patient meets one of the following (A or B):

A) Generic voriconazole tablets or oral suspension is requested; OR

B) Patient meets both of the following (i and ii):

iii. Patient has tried the corresponding generic voriconazole product (tablet or oral suspension); AND

iv. Patient cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescriber, would result in a significant allergy or serious adverse reaction.

11. Fungal Infection (Systemic) in a Patient with Human Immunodeficiency Virus (HIV) – Prophylaxis or Treatment. Approve for 6 months if the patient meets one of the following (A or B):

A) Generic voriconazole tablets or oral suspension is requested; OR

B) Patient meets both of the following (i and ii):

i. Patient has tried the corresponding generic voriconazole product (tablet or oral suspension); AND

ii. Patient cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescriber, would result in a significant allergy or serious adverse reaction.

12. Oropharyngeal Candidiasis (Fluconazole-Refractory) – Treatment. Approve for 3 months if the patient meets one of the following (A or B):

A) Generic voriconazole tablets or oral suspension is requested; OR

B) Patient meets both of the following (i and ii):

i. Patient has tried the corresponding generic voriconazole product (tablet or oral suspension); AND

ii. Patient cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the

bioequivalent generic product, which per the prescriber, would result in a significant allergy or serious adverse reaction.

13. **Fungal Infection (Systemic) that is Susceptible to Voriconazole – Treatment.** Approve for 3 months if the patient meets one of the following (A or B):
    - **A)** Generic voriconazole tablets or oral suspension is requested; OR
    - **B)** Patient meets both of the following (i and ii):
        - **i.** Patient has tried the corresponding generic voriconazole product (tablet or oral suspension); AND
        - **ii.** Patient cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescriber, would result in a significant allergy or serious adverse reaction.

14. **Patient is Currently Receiving Voriconazole.** Approve for 3 months to complete the course of therapy if the patient meets ONE of the following (A or B):
    - **A)** Generic voriconazole tablets or oral suspension is requested; OR
    - **B)** Patient meets both of the following (i and ii):
        - **i.** Patient has tried the corresponding generic voriconazole product (tablet or oral suspension); AND
        - **ii.** Patient cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescriber, would result in a significant allergy or serious adverse reaction.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vfend/voriconazole is not recommended in the following situations:

13. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

24. Vfend® tablet and oral suspension [prescribing information]. New York, NY: Roerig/Pfizer; January 2019.
25. Patterson TF, Thompson GR, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2016;63(4):e1-e60.
26. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guidelines for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2016;62(4):e1-50.
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30. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-oi/guidelines-adult-adolescent-oi.pdf h. Last updated June 14, 2023. Accessed on July 19, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Antiseizure Medications – Clobazam Products Prior Authorization Policy
- Onfi® (clobazam tablets and oral suspension – Lundbeck, generic)
- Sympazan® (clobazam oral soluble film – Aquestive Therapeutics)

REVIEW DATE: 11/15/2023

OVERVIEW

All forms of clobazam are indicated for the adjunctive treatment of seizures associated with **Lennox-Gastaut syndrome** (LGS) in patients ≥ 2 years of age.[1,2]

Disease Overview

LGS, a severe epileptic and developmental encephalopathy, is associated with a high rate of morbidity and mortality.[3,4] LGS most often begins between 3 and 5 years of age and comprises approximately 4% to 10% of childhood epilepsies; the prevalence is 0.26 per 1,000 people.[3-6] Affected children experience several different types of seizures, most commonly atonic seizures (sudden loss of muscle tone and limpness, also called drop seizures) and tonic seizures (increased muscle tone and muscle stiffness).[3,6] Seizures associated with LGS are usually resistant to treatment.[6] The three main forms of treatment of LGS are antiseizure medications (ASMs), dietary therapy (typically the ketogenic diet), and device/surgery (e.g., vagus nerve stimulation, corpus callosotomy).[6] None of the therapies are effective in all cases of LGS and the disorder has proven particularly resistant to most therapeutic options. The choice of treatment should take into consideration the patient's age and other associated conditions.

Other Uses with Supportive Evidence

Dravet syndrome is a rare genetic epileptic encephalopathy (dysfunction of the brain) marked with frequent and/or prolonged seizures.[7,8] It has been estimated that 1 out of 15,700 infants born in the US are affected with Dravet syndrome. The seizures generally begin in the first year of life in an otherwise healthy infant. Affected individuals can develop many seizure types: myoclonic, tonic-clonic, absence, atypical absence, atonic, focal aware or impaired awareness (previously called partial seizures), and status epilepticus.[8] As the seizures continue, most of the children develop some level of developmental disability and other conditions associated with the syndrome. Two or more ASMs are often needed to control the seizures; most of the seizures are refractory to medications. The goals of treatment are cessation of prolonged convulsions, reductions in overall seizure frequency, and minimization of treatment side effects.[9,10] Some patients respond to the ketogenic diet and/or vagus nerve stimulation.

Guidelines/Recommendations

The American Academy of Neurology and the American Epilepsy Society published a guideline update for treatment-resistant epilepsy (2018) stating that clobazam is probably effective as add-on therapy for LGS and is possibly effective as add-on therapy for treatment-resistant adult focal epilepsy.[13] Adjunctive therapy with clobazam has been effective in the treatment of uncontrolled or refractory epilepsy in adults and children.[14] If first-line treatment is ineffective or not tolerated, clobazam has been used as adjunctive treatment of refractory focal seizures (partial seizure and localization-related seizure) in children, young adults, and adults; adjunctive treatment of generalized tonic-clonic seizures in children, young adults, and adults; and adjunctive treatment of children and young adults with benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome or late-onset childhood occipital epilepsy (Gastaut type).

A) *Lennox-Gastaut Syndrome*

B) Currently, the FDA-approved drugs for this condition are Epidiolex® (cannabidiol oral solution), felbamate, lamotrigine, rufinamide tablets and oral suspension, topiramate, clobazam, and Fintepla® (fenfluramine oral solution).[11,14] Despite the lack of level I or level II evidence, valproic acid remains a mainstay in treatment.[5,6,12] If valproic acid does not provide adequate seizure control, which is almost always the case, lamotrigine should be added as the first adjunctive therapy.[4] If the combination regimen of valproic acid and lamotrigine does not provide adequate control, then rufinamide should be initiated and either valproic acid or lamotrigine should be discontinued. If seizure control is still not achieved, the next adjunctive therapies to consider are topiramate, clobazam, and felbamate. There is limited evidence for the use of levetiracetam, zonisamide, and Fycompa® (perampanel tablet, oral suspension). Where possible, no more than two ASMs should be used concomitantly; use of multiple ASMs raises the risk of adverse effects and/or drug-drug interactions.

Dravet Syndrome

Valproic acid and clobazam are considered to be the first-line treatment for Dravet syndrome.[7,9,10] If seizure control is suboptimal, Diacomit® (stiripentol capsules), Epidiolex, Fintepla, and topiramate are treatment options. If control is still inadequate, other therapies to consider are clonazepam, levetiracetam, and zonisamide. Drugs that should be avoided in Dravet syndrome include sodium channel blockers (e.g., carbamazepine, oxcarbazepine, lamotrigine, and phenytoin), Sabril® (vigabatrin tablet, oral packet), and tiagabine.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of clobazam. Because of the specialized skills required for evaluation and diagnosis of patients treated with clobazam as well as the monitoring required for adverse events and long-term efficacy, initial approval requires clobazam to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of clobazam is recommended in those who meet one of the following criteria:

FDA-Approved Indication

8. Lennox-Gastaut Syndrome. Approve for 1 year if the patient meets ONE of the following (A or B):

- **A)** Initial Therapy. Approve if the patient meets the following (i, ii, and iii):
  - **i.** Patient is ≥ 2 years of age; AND
  - **ii.** Patient has tried and/or is concomitantly receiving one of the following (a or b):
    - **a)** At least two other antiseizure medications; OR
      Note: Examples of other antiseizure medications include valproic acid, levetiracetam, zonisamide, Fycompa (perampanel), vigabatrin, others.
    - **b)** One of lamotrigine, topiramate, rufinamide, felbamate, Fintepla (fenfluramine oral solution), or Epidiolex (cannabidiol oral solution); AND
  - **iii.** Clobazam is prescribed by or in consultation with a neurologist.
- **B)** Patient is Currently Receiving Clobazam. Approve if the patient is responding to therapy, as determined by the prescriber.

Note: Examples of therapy response include reduced seizure severity, frequency, and/or duration from baseline (prior to initiation of clobazam).

Other Uses with Supportive Evidence

9. Dravet Syndrome. Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets the following (i and ii):

i. Patient is ≥ 2 years of age; AND

ii. Clobazam is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Clobazam. Approve if the patient is responding to therapy, as determined by the prescriber.

Note: Examples of therapy response include reduced seizure severity, frequency, and/or duration from baseline (prior to initiation of clobazam).

3. Treatment-Refractory Seizures/Epilepsy. Approve for 1 year if the patient meets ONE of the following (A or B):

C) Initial Therapy. Approve if the patient meets the following (i, ii, and iii):

i. Patient is ≥ 2 years of age; AND

ii. Patient has tried and/or is concomitantly receiving at least two other antiseizure medications; AND

Note: Examples of other antiseizure medications are valproic acid, lamotrigine, topiramate, clonazepam, levetiracetam, zonisamide, rufinamide, felbamate.

iii. Clobazam is prescribed by or in consultation with a neurologist.

D) Patient is Currently Receiving Clobazam. Approve if the patient is responding to therapy, as determined by the prescriber.

Note: Examples of therapy response include reduced seizure severity, frequency, and/or duration from baseline (prior to initiation of clobazam).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of clobazam is not recommended in the following situations:

14. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Antiseizure Medications – Diacomit Prior Authorization Policy
- Diacomit® (stiripentol capsules and powder for oral suspension – Biocodex)

REVIEW DATE: 02/15/2023

OVERVIEW

Diacomit, an antiseizure medication (ASM), is indicated for the treatment of seizures associated with **Dravet syndrome** in patients ≥ 6 months of age and weighing ≥ 7 kg taking clobazam.[1] There are no clinical data to support the use of Diacomit as monotherapy in Dravet syndrome.

Disease Overview

Dravet syndrome is a rare genetic epileptic encephalopathy (dysfunction of the brain) marked with frequent and/or prolonged seizures.[2,3] The seizures generally begin in the first year of life in an otherwise healthy infant. Affected individuals can develop many seizure types: myoclonic, tonic-clonic, absence, atypical absence, atonic, focal aware or impaired awareness (previously called partial seizures), and status epilepticus.[3] Two or more ASMs are often needed to control the seizures; most of the seizures are refractory to medications. The goals of treatment are cessation of prolonged convulsions, reduction in overall seizure frequency, and minimization of treatment side effects.[4,5]

Clinical Efficacy in Other Refractory Seizures

In one study (n = 212), Diacomit was studied in children with different types of epilepsy syndromes (including Lennox-Gastaut Syndrome [LGS]; infantile spasms; infection-related or anoxo-ischemic epilepsy syndromes; tuberous sclerosis complex; Sturge-Weber syndrome; Doose syndrome; cortical malformation/dysplasia; and epilepsy with myoclonic absences) whose seizures were refractory to more than two ASMs (including vigabatrin).[6] In the 88 patients who completed the 3-month placebo-controlled study, 56.8% of patients with partial epilepsy responded (with 14% becoming seizure-free) compared with 41.9% of patients with generalized epilepsy and 38.4% of patients with myoclonic epilepsy. Diacomit has also been administered to patients with epileptic encephalopathies associated with sodium voltage-gated channel alpha subunit 1 (SCN1A) mutations or other sodium channel mutations under compassionate use protocols.[7] A single-blind, exploratory trial evaluated Diacomit in combination with standard treatment in 16 patients with LGS and eight patients with symptomatic generalized epilepsy of the Lennox-Gastaut type.[8] There were 15 evaluable patients with LGS. The overall results identified some benefit for LGS where 60% of patients were responders (based on 50% responder rate). Diacomit treatment produced a mean 62% seizure reduction and median 80% reduction from baseline. Additionally, a published study of Diacomit added to carbamazepine in childhood partial epilepsy (n = 67) demonstrated seizure response in 32 patients with conditions including herpetic encephalitis, LGS, and tuberous sclerosis complex.[9]

Guidelines/Recommendations

At this time, there are three drugs approved for the treatment of seizures associated with Dravet syndrome: Diacomit, Epidiolex® (cannabidiol oral solution), and Fintepla® (fenfluramine oral solution).[1,10,11] An expert panel considers valproic acid and clobazam to be the first-line treatment for Dravet syndrome.[5] If seizure control is suboptimal, Diacomit and topiramate are second-line treatment. Ketogenic diet is moderately effective and can also be considered second-line. The Dravet Foundation states that Diacomit, Epidiolex, and Fintepla are considered first-line agents for the treatment of Dravet syndrome.[2] If control is still inadequate, other therapies to consider are clonazepam, levetiracetam, and zonisamide.[2,4,5] Sodium channel blockers (e.g., carbamazepine, oxcarbazepine, lamotrigine, and phenytoin) can worsen seizures in

Dravet syndrome. Additionally, vigabatrin and tiagabine may increase the frequency of myoclonic seizures and should be avoided.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Diacomit. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Diacomit as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Diacomit to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Diacomit is recommended in those who meet one of the following criteria:

FDA-Approved Indication

10. Dravet Syndrome. Approve for 1 year if the patient meets ONE of the following criteria (A or B):

C) Initial Therapy: Approve if the patient meets the following criteria (i, ii, and iii):

i. Patient is ≥ 6 months of age and weighs ≥ 7 kg; AND

ii. Patient meets ONE of the following criteria (a or b):

a) Patient is taking concomitant clobazam; OR

b) Patient is unable to take clobazam due to adverse events as determined by the prescriber; AND

iii. The medication is prescribed by or in consultation with a neurologist; OR

D) Patient is Currently Receiving Diacomit: Approve if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

Other Uses with Supportive Evidence

2. Treatment-Refractory Seizures/Epilepsy (specific rare conditions) [i.e., Lennox-Gastaut Syndrome; infantile spasms; tuberous sclerosis complex; Sturge-Weber syndrome; Doose syndrome; infection-related or anoxo-ischemic epilepsy syndromes; cortical malformation/dysplasia; epileptic encephalopathies associated with sodium channel mutations; and epilepsy with myoclonic absences]. Approve for 1 year if the patient meets ONE of the following criteria (A or B):

E) Initial Therapy: Approve if the patient meets the following criteria (i, ii, and iii):

i. Patient is ≥ 6 months of age and weighs ≥ 7 kg; AND

ii. Patient has tried at least two other antiseizure medications; AND

F) Note: Examples of other antiseizure medications include valproic acid, lamotrigine, topiramate, clonazepam, Banzel® (rufinamide tablet, oral suspension), felbamate, clobazam, Fycompa® (perampanel tablet, oral suspension), vigabatrin, levetiracetam, zonisamide.

iii. The medication is prescribed by or in consultation with a neurologist; OR

G) Patient is Currently Receiving Diacomit: Approve if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Diacomit is not recommended in the following situations:

15. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Antiseizure Medications – Epidiolex Prior Authorization Policy
- Epidiolex® (cannabidiol oral solution – Greenwich Biosciences)

REVIEW DATE: 02/15/2023

OVERVIEW

Epidiolex, a cannabinoid, is indicated in patients ≥ 1 year of age for the **treatment of seizures associated with**:[1]

- **Dravet syndrome**.
- **Lennox-Gastaut syndrome**.
- **Tuberous sclerosis complex**.

Disease Overview

Dravet syndrome is a rare genetic epileptic encephalopathy marked with frequent and/or prolonged seizures.[2,3] The seizures generally begin in the first year of life in an otherwise healthy infant. Affected individuals can develop many seizure types: myoclonic, tonic-clonic, absence, atypical absence, atonic, focal aware or impaired awareness (previously called partial seizures), and status epilepticus.[3] Two or more antiseizure medications (ASMs) are often needed to control the seizures; most of the seizures are refractory to medications. The goals of treatment are cessation of prolonged convulsions, reduction in overall seizure frequency, and minimization of treatment side effects.[4,5]

Lennox-Gastaut syndrome, a severe epileptic and developmental encephalopathy, is associated with a high rate of morbidity and mortality.[6,7] Lennox-Gastaut syndrome most often begins between 3 and 5 years of age.[6-9] Affected children experience several different types of seizures, most commonly atonic seizures (sudden loss of muscle tone and limpness) and tonic seizures.[6,9] The three main forms of treatment of Lennox-Gastaut syndrome are ASMs, dietary therapy (typically the ketogenic diet), and device/surgery (e.g., vagus nerve stimulation, corpus callostomy).[9] None of the therapies are effective in all cases of Lennox-Gastaut syndrome and the disorder has proven particularly resistant to most therapeutic options.

Tuberous sclerosis complex is a rare, genetic disease that causes non-cancerous (benign) tumors to grow in the brain and on other vital organs such as the kidneys, heart, eyes, lungs, and skin.[10] It can result in a combination of symptoms including seizures, impaired intellectual development, autism, behavioral problems, skin abnormalities, and kidney disease. Seizures affect most individuals with tuberous sclerosis complex at some point during their life and can be difficult to control.

Clinical Efficacy in Other Refractory Seizures

A) In 2014, an expanded access program was initiated to provide Epidiolex to patients with treatment-resistant epilepsy. Of the 607 patients included in a published review, 174 patients were diagnosed with Dravet syndrome or Lennox-Gastaut syndrome, and 433 patients were diagnosed with other conditions, including CDKL5 deficiency disorder, Dup15q, Aicardi, and Doose syndromes; febrile infection-related epilepsy syndromes; tuberous sclerosis complex; Sturge-Weber syndrome; lissencephaly; cortical malformation/dysplasia; and myoclonic absence.[14] The patients enrolled in the study had severe, intractable, childhood-onset treatment-resistant epilepsy and were on stable doses of ASMs for 4 weeks before starting Epidiolex as add-on therapy. The initial dose of Epidiolex was 2 to 10 mg/kg/day (taken as two divided doses) and gradually titrated until intolerance or to a maximum dose of 25 mg/kg/day or 50 mg/kg/day, depending upon treatment site. After 12 weeks of treatment, Epidiolex was associated with

51% and 48% reductions in median monthly convulsive and total seizures, respectively. In a cohort of 132 patients (72 children, 60 adults) with treatment-resistant epilepsy, bi-weekly seizure frequency decreased from a mean of 144.4 at entry to 52.2 at 12 weeks (P = 0.01) and remained stable thereafter.[15] Of note, patients with a diagnosis of Lennox-Gastaut syndrome or Dravet syndrome were initially excluded because of preferential enrollment into the randomized clinical trials; once these trials were closed for enrollment, patients with these syndromes were also enrolled. In a separate cohort of patients with CDKL5 deficiency disorder and Aicardi, Doose, and Dup15q syndromes (n = 46), the percent change in median convulsive seizure frequency decreased from baseline to Week 12 by 51.4% and by 59.1% at Week 48.[16] There was a significant difference between the percent changes in monthly convulsive seizure frequency during baseline and Week 12 (P = 0.00001), with no difference in seizure percent change between Weeks 12 and 48. Of the 55 patients in the safety group, 27% of patients withdrew by Week 144 due to adverse effects (n = 4), lack of efficacy (n = 9), withdrawn consent (n = 1), and lost to follow-up (n = 1).

Guidelines/Recommendations

Dravet Syndrome

At this time, there are three drugs approved for the treatment of seizures associated with Dravet syndrome: Epidiolex, Diacomit® (stiripentol capsules, powder for oral suspension), and Fintepla® (fenfluramine oral solution).[1,11,17] An expert panel considers valproic acid and clobazam to be the first-line treatment for Dravet syndrome.[4] If seizure control is suboptimal, Diacomit and topiramate are second-line treatment. Ketogenic diet is moderately effective and can also be considered second-line. The Dravet Foundation states that Diacomit, Epidiolex, and Fintepla are considered first-line agents for the treatment of Dravet syndrome.[2] If control is still inadequate, other therapies to consider are clonazepam, levetiracetam, and zonisamide.[2,4] Sodium channel blockers (e.g., carbamazepine, oxcarbazepine, lamotrigine, and phenytoin) can worsen seizures in Dravet syndrome. Additionally, vigabatrin and tiagabine may increase the frequency of myoclonic seizures and should be avoided.

Lennox-Gastaut Syndrome

Currently, the FDA-approved drugs for this condition are Epidiolex, Fintepla, felbamate, Banzel® (rufinamide tablet, oral suspension), lamotrigine, topiramate, and clobazam.[12] Despite the lack of level I or level II evidence, valproic acid remains a mainstay in treatment.[8,9,13] If valproic acid does not provide adequate seizure control, which is almost always the case, lamotrigine should be added as the first adjunctive therapy.[7] If the combination regimen of valproic acid and lamotrigine does not provide adequate control, then Banzel should be initiated and either valproic acid or lamotrigine should be discontinued. If seizure control is still not achieved, the next adjunctive therapies to consider are topiramate, clobazam, and felbamate. There is limited evidence for the use of levetiracetam, zonisamide, and Fycompa® (perampanel tablet, oral suspension). Where possible, no more than two ASMs should be used concomitantly; use of multiple ASMs raise the risk of side effects and/or drug-drug interactions.

POLICY STATEMENT

66. Prior Authorization is recommended for prescription benefit coverage of Epidiolex. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Epidiolex as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Epidiolex to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Epidiolex is recommended in those who meet the following criteria:

FDA-Approved Indications

11. Dravet Syndrome. Approve if the patient meets ONE of the following criteria (A or B):
- **E)** Initial Therapy. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
  - **iv.** Patient is ≥ 1 year of age; AND
  - **v.** Patient meets ONE of the following criteria (a or b):
    - i. Patient has tried or is concomitantly receiving at least two other antiseizure medications; OR
      Note: Examples of other antiseizure medications include valproic acid, topiramate, clonazepam, levetiracetam, zonisamide.
    - ii. Patient has tried or is concomitantly receiving one of Fintepla, Diacomit or clobazam; AND
  - **vi.** The medication is prescribed by or in consultation with a neurologist.
- **F)** Patient is Currently Receiving Epidiolex. Approve for 1 year if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.
- **B)**

12. Lennox-Gastaut Syndrome. Approve if the patient meets ONE of the following criteria (A or B):
- **C)** Initial Therapy. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
  - **i.** Patient is ≥ 1 year of age; AND
  - **ii.** Patient has tried or is concomitantly receiving at least two other antiseizure medications; AND
    Note: Examples of other antiseizure medications include lamotrigine, topiramate, Banzel, felbamate, clobazam, valproic acid, levetiracetam, zonisamide, Fycompa, vigabatrin.
  - **iii.** The medication is prescribed by or in consultation with a neurologist.
- **D)** Patient is Currently Receiving Epidiolex. Approve for 1 year if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

13. Tuberous Sclerosis Complex. Approve if the patient meets ONE of the following criteria (A or B):
- **A)** Initial Therapy. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
  - **i.** Patient is ≥ 1 year of age; AND
  - **ii.** Patient has tried or is concomitantly receiving at least two other antiseizure medications; AND
    Note: Examples of other antiseizure medications include valproic acid, lamotrigine, topiramate, clonazepam, levetiracetam, zonisamide, Banzel, felbamate, clobazam, Fycompa, vigabatrin, everolimus.
  - **iii.** The medication is prescribed by or in consultation with a neurologist.
- **B)** Patient is Currently Receiving Epidiolex. Approve for 1 year if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

Other Uses with Supportive Evidence

4. Treatment-Refractory Seizures/Epilepsy [specific rare conditions] (i.e., CDKL5 deficiency disorder; Dup15q, Aicardi, or Doose syndromes; febrile infection-related epilepsy syndromes; Sturge-Weber syndrome; lissencephaly; cortical malformation/dysplasia; and epilepsy with myoclonic absences). Approve if the patient meets ONE of the following criteria (A or B):
- **H)** Initial Therapy. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
  - **iv.** Patient is ≥ 1 year of age; AND
  - **v.** Patient has tried or is concomitantly receiving at least two other antiseizure medications; AND
    C) Note: Examples of other antiseizure medications include valproic acid, lamotrigine, topiramate, clonazepam, levetiracetam, zonisamide, Banzel, felbamate, clobazam, Fycompa, vigabatrin.
  - **vi.** The medication is prescribed by or in consultation with a neurologist.

I) Patient is Currently Receiving Epidiolex. Approve for 1 year if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Epidiolex is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Antiseizure Medications – Fintepla Prior Authorization Policy
- Fintepla® (fenfluramine oral solution – Zogenix)

REVIEW DATE: 04/19/2023

OVERVIEW

Fintepla, a serotonin 5-hydroxytryptamine subtype 2 (5-HT_2) agonist, is indicated in patients ≥ 2 years of age for the treatment of **seizures associated with:**
- **Dravet syndrome**.
- **Lennox-Gastaut syndrome**.

Disease Overview

Dravet syndrome is a rare genetic epileptic encephalopathy (dysfunction of the brain) marked with frequent and/or prolonged seizures.[2,3] It is estimated that 1 out of 15,700 infants born in the US are affected with Dravet syndrome. The seizures generally begin in the first year of life in an otherwise healthy infant. Affected individuals can develop many seizure types: myoclonic, tonic-clonic, absence, atypical absence, atonic, focal aware or impaired awareness (previously called partial seizures), and status epilepticus.[3] As the seizures continue, most of the children develop some level of developmental disability and other conditions associated with the syndrome. Two or more antiseizure medications (ASMs) are often needed to control the seizures; most of the seizures are refractory to medications. The goals of treatment are cessation of prolonged convulsions, reductions in overall seizure frequency, and minimization of treatment side effects.[4,5] Some patients respond to the ketogenic diet and/or vagus nerve stimulation.

Lennox-Gastaut syndrome, a severe epileptic and developmental encephalopathy, is associated with a high rate of morbidity and mortality.[6,7] Lennox-Gastaut syndrome most often begins between 3 and 5 years of age.[6-9] Affected children experience several different types of seizures, most commonly atonic seizures (sudden loss of muscle tone and limpness) and tonic seizures.[6,9] The three main forms of treatment of Lennox-Gastaut syndrome are ASMs, dietary therapy (typically the ketogenic diet), and device/surgery (e.g., vagus nerve stimulation, corpus callostomy).[9] None of the therapies are effective in all cases of Lennox-Gastaut syndrome and the disorder has proven particularly resistant to most therapeutic options.

Guidelines

Fintepla is not mentioned in the current treatment recommendations.

Dravet Syndrome

At this time, there are three drugs approved for the treatment of seizures associated with Dravet syndrome: Diacomit® (stiripentol capsules, powder for oral suspension), Epidiolex® (cannabidiol oral solution), and Fintepla.[1,10] An expert panel considers valproic acid to be the first-line treatment for Dravet syndrome.[4] Clobazam, Diacomit, and Fintepla can be considered as either first- or second-line ASMs. Cannabidiol was supported either as first- or second-line treatment. There was modest consensus among caregivers, but no consensus among physicians to support topiramate as first-, second-, or third-line therapy. The Dravet Foundation states that Diacomit, Epidiolex, and Fintepla are considered first-line agents for the treatment of Dravet syndrome.[2] If control is still inadequate, other therapies to consider are clonazepam, levetiracetam, and zonisamide.[2,4] Sodium channel blockers (e.g., carbamazepine, oxcarbazepine, lamotrigine, and phenytoin) can worsen seizures in Dravet syndrome. Additionally, vigabatrin and tiagabine may increase the frequency of myoclonic seizures and should be avoided.

Lennox-Gastaut Syndrome
Currently, the FDA-approved drugs for this condition are Fintepla, clobazam, clonazepam, Banzel® (rufinamide tablet, oral suspension), Epidiolex, felbamate, lamotrigine, and topiramate. Despite the lack of level I or level II evidence, valproic acid remains a mainstay in treatment.[8,9,12] If valproic acid does not provide adequate seizure control, which is almost always the case, lamotrigine should be added as the first adjunctive therapy.[7] If the combination regimen of valproic acid and lamotrigine does not provide adequate control, then Banzel should be initiated and either valproic acid or lamotrigine should be discontinued. If seizure control is still not achieved, the next adjunctive therapies to consider are topiramate, clobazam, and felbamate. There is limited evidence for the use of levetiracetam, zonisamide, and Fycompa® (perampanel tablet, oral suspension). Where possible, no more than two ASMs should be used concomitantly; use of multiple ASMs raise the risk of side effects and/or drug-drug interactions.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Fintepla. Because of the specialized skills required for evaluation and diagnosis of patients treated with Fintepla as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Fintepla to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Fintepla is recommended in those who meet the following criteria:

FDA-Approved Indications

16. Dravet Syndrome. Approve if the patient meets ONE the following criteria (A or B):
- **A)** Initial Therapy. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
  - **i.** Patient is ≥ 2 years of age; AND
  - **ii.** Patient meets ONE of the following criteria (a or b):
    - **a)** Patient has tried or is concomitantly receiving at least two other antiseizure medications; OR
      Note: Examples of other antiseizure medications include valproic acid, topiramate, clonazepam, levetiracetam, zonisamide.
    - **b)** Patient has tried or is concomitantly receiving one of clobazam, Epidiolex or Diacomit; AND
  - **iii.** Fintepla is prescribed by or consultation with a neurologist; OR
- **B)** Patient is Currently Receiving Fintepla. Approve for 1 year if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

17. Lennox-Gastaut Syndrome. Approve if the patient meets ONE of the following criteria (A or B):
- **E)** Initial Therapy. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
  - **i.** Patient is ≥ 2 years of age; AND
  - **ii.** Patient has tried or is concomitantly receiving at least two other antiseizure medications; AND
    Note: Examples of other antiseizure medications include Banzel, clobazam, Epidiolex, felbamate, lamotrigine, topiramate, valproic acid, levetiracetam, zonisamide, Fycompa, vigabatrin.

iii. The medication is prescribed by or in consultation with a neurologist.

F) Patient is Currently Receiving Fintepla. Approve for 1 year if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Fintepla is not recommended in the following situations:

15. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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68. Knupp KG1, Wirrell EC. Treatment Strategies for Dravet Syndrome. *CNS Drugs*. 2018;32(4):335-350.
69. Sirven JI, Shafer PO. Epilepsy Foundation – Lennox-Gastaut Syndrome. Updated February 2020. Available at: https://www.epilepsy.com/learn/types-epilepsy-syndromes/lennox-gastaut-syndrome-lgs. Accessed on April 17, 2023.
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72. Wheless JW. National Organization for Rare Diseases (NORD) – Lennox-Gastaut syndrome. Available at: https://rarediseases.org/rare-diseases/lennox-gastaut-syndrome/#standard-therapies. Accessed on April 17, 2023.
73. Diacomit® capsules, powder for oral suspension [prescribing information]. Redwood City, CA: Bicodex; July 2022.
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PRIOR AUTHORIZATION POLICY

POLICY: Antiseizure Medications – Nayzilam Prior Authorization Policy
- Nayzilam® (midazolam nasal spray – UCB)

REVIEW DATE: 09/20/2023

OVERVIEW

Nayzilam, a benzodiazepine, is indicated for the acute treatment of **intermittent, stereotypic episodes of frequent seizure activity** (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 12 years of age.[1]

Disease Overview

Patients with epilepsy can experience acute repetitive seizures or seizure clusters.[2] No consensus definition of a seizure cluster has been agreed upon.[3] A broad definition of seizure clusters has been proposed to be "acute episodes of deterioration in seizure control". More specifically, they could be defined as a series of grouped seizures that have short interictal periods. However, the number of seizures and the interictal period are the subject of controversy. Seizure clusters can result in increased emergency room visits or hospitalization, and they can disrupt the daily life, studies, and work of patients and caregivers. They are particularly concerning because of their association with status epilepticus, a potentially life-threatening condition. Benzodiazepine rescue medication is the primary acute therapy for management of seizure clusters, helping to abort clusters and reduce emergency department visits.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Nayzilam. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nayzilam as well as the monitoring required for adverse events and efficacy, approval requires Nayzilam to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nayzilam is recommended in those who meet the following criteria:

FDA-Approved Indication

18. Intermittent Episodes of Frequent Seizure Activity (i.e., seizure clusters, acute repetitive seizures). Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient is currently receiving maintenance antiseizure medication(s); AND
- **B)** The medication is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nayzilam is not recommended in the following situations:

16. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

76. Nayzilam® nasal spray [prescribing information]. Smyrna, GA: UCB; January 2023.

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78. Chung S, Szaflarski JP, Choi EJ, et al. A systematic review of seizure clusters: Prevalence, risk factors, burden of disease and treatment patterns. *Epilepsy Res*. 2021;177:106748.

PRIOR AUTHORIZATION POLICY

POLICY: Antiseizure Medications – Rufinamide Prior Authorization Policy
- Banzel® (rufinamide tablets and oral suspension – Eisai, generic)

REVIEW DATE: 09/20/2023

OVERVIEW

Rufinamide is indicated for adjunctive treatment of **seizures associated with Lennox-Gastaut syndrome** (LGS) in patients ≥ 1 year of age.[1]

Although rufinamide is only FDA-approved for use in LGS, clinical trial data indicate the drug may also be beneficial as adjunctive treatment of refractory focal epilepsy.[2] A review of six clinical trials found that rufinamide when used as an add-on treatment was effective in reducing seizure frequency in patients with drug-resistant focal epilepsy.

Disease Overview

LGS is a severe epileptic and developmental encephalopathy associated with a high rate of morbidity and mortality.[3,4] LGS most often begins between 3 years and 5 years of age and comprises approximately 3% to 4% of childhood epilepsies.[3-6] Affected children experience several different types of seizures, most commonly atonic seizures (sudden loss of muscle tone and limpness, also called drop seizures) and tonic seizures (increased muscle tone and muscle stiffness).[3,6] The three main forms of treatment of LGS are antiseizure medications (ASMs), dietary therapy (typically the ketogenic diet), and device/surgery (e.g., vagus nerve stimulation, corpus callosotomy).[6] None of the therapies are effective in all cases of LGS and the disorder has proven particularly resistant to most therapeutic options. The choice of treatment should take into consideration the patient's age and other associated conditions.

Guidelines/Recommendations

16. Lennox-Gastaut syndrome: Currently, the FDA-approved drugs for this condition are Epidiolex® (cannabidiol oral solution), felbamate, lamotrigine, rufinamide, topiramate, and clobazam.[7] Despite the lack of level I or level II evidence, valproic acid remains a mainstay in treatment.[5,6,8] If valproic acid does not provide adequate seizure control, which is almost always the case, lamotrigine should be added as the first adjunctive therapy.[4] If the combination regimen of valproic acid and lamotrigine does not provide adequate control, then rufinamide should be initiated and either valproic acid or lamotrigine should be discontinued. If seizure control is still not achieved, the next adjunctive therapies to consider are topiramate, clobazam, and felbamate. There are limited evidence for the use of levetiracetam, zonisamide, and Fycompa® (perampanel tablets and oral suspension). Where possible, no more than two ASMs should be used concomitantly; use of multiple ASMs raise the risk of side effects and/or drug-drug interactions.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of rufinamide. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with rufinamide as well as the monitoring required for adverse events and long-term efficacy, initial approval requires rufinamide to be prescribed by, or in consultation with, a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of rufinamide is recommended in those who meet one of the following criteria:

FDA-Approved Indication

14. Lennox-Gastaut Syndrome. Approve for 1 year if the patient meets ONE of the following (A or B):

G) Initial Therapy. Approve if the patient meets the following (i, ii, and iii):

i. Patient is ≥ 1 year of age; AND

ii. Patient has tried and/or is concomitantly receiving at least two other antiseizure medications; AND

Note: Examples of antiseizure medications include valproic acid, gabapentin, phenytoin, carbamazepine, oxcarbazepine, lacosamide, levetiracetam, zonisamide, Fycompa (perampanel tablet or oral suspension), vigabatrin, lamotrigine, topiramate, clobazam, Diacomit (stiripentol capsules or oral suspension), Epidiolex (cannabidiol oral solution), and felbamate.

iii. The medication is prescribed by or in consultation with a neurologist.

H) Patient is Currently Receiving rufinamide. Approve if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

Other Uses with Supportive Evidence

5. Treatment-Refractory Seizures/Epilepsy. Approve for 1 year if the patient meets ONE of the following (A or B):

J) Initial Therapy. Approve if the patient meets the following (i, ii, and iii):

vii. Patient is ≥ 1 years of age; AND

viii. Patient has tried and/or is concomitantly receiving at least two other antiseizure medications; AND

Note: Examples of antiseizure medications include valproic acid, gabapentin, phenytoin, carbamazepine, oxcarbazepine, lacosamide, levetiracetam, zonisamide, Fycompa (perampanel tablet or oral suspension), vigabatrin, lamotrigine, topiramate, clobazam, Diacomit (stiripentol capsules or oral suspension), Epidiolex (cannabidiol oral solution), and felbamate.

ix. The medication is prescribed by or in consultation with a neurologist.

K) Patient is Currently Receiving rufinamide. Approve if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of rufinamide is not recommended in the following situations:

17. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

56. Banzel® tablets and oral suspension [prescribing information]. Woodcliff Lake, NJ: Eisai; November 2019.
57. Brigo F, Jones K, Eltze C, et al. Anti-seizure medications for Lennox-Gastaut syndrome. *Cochrane Database Syst Rev.* 2021;4(4):CD003277.
58. Sirven JI, Shafer PO. Epilepsy Foundation – Lennox-Gastaut Syndrome. Updated February 2020. Available at: https://www.epilepsy.com/learn/types-epilepsy-syndromes/lennox-gastaut-syndrome-lgs. Accessed on September 14, 2023.

59. Cross JH, Auvin S, Falip M, et al. Expert opinion on the management of Lennox-Gastaut syndrome: treatment algorithms and practical considerations. *Front Neurol*. 2017;8:505.
60. Ostendorf AP, Ng YT. Treatment-resistant Lennox-Gastaut syndrome: therapeutic trends, challenges, and future directions. *Neuropsych Dis Treatment*. 2017;13:1131-1140.
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PRIOR AUTHORIZATION POLICY

POLICY: Antiseizure Medications – Valtoco Prior Authorization Policy
- Valtoco® (diazepam nasal spray – Neurelis)

REVIEW DATE: 02/15/2023

OVERVIEW

Valtoco, a benzodiazepine, is indicated for the acute treatment of **intermittent, stereotypic episodes of frequent seizure activity** (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 6 years of age.[1]

Valtoco is for acute treatment only. Do not use more than two doses of Valtoco to treat a single episode.[1] It is recommended that Valtoco be used to treat no more than one episode every 5 days and no more than five episodes per month.

Disease Overview

Patients with epilepsy can experience acute repetitive seizures or seizure clusters.[2] Patients with severe and/or poorly controlled epilepsy are more likely to experience seizure clusters. Seizure clusters can result in increased emergency room visits or hospitalization, and they can disrupt the daily life, studies, and work of patients and caregivers. They are particularly concerning because of their association with status epilepticus, a potentially life-threatening condition. Benzodiazepine rescue medication is the primary acute therapy for management of seizure clusters, helping to abort clusters and reduce emergency department visits.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Valtoco. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Valtoco is recommended in those who meet the following criteria:

FDA-Approved Indication

19. Intermittent Episodes of Frequent Seizure Activity (i.e., seizure clusters, acute repetitive seizures). Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient is currently receiving maintenance antiseizure medication(s); AND
- **B)** The medication is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Valtoco is not recommended in the following situations:

17. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

79. Valtoco® nasal spray [prescribing information]. San Diego, CA: Neurelis; January 2023.

80. Jafarpour S, Hirsch LJ, Gaínza-Lein M, et al. Seizure cluster: Definition, prevalence, consequences, and management. *Seizure*. 2019;68:9-15.

PRIOR AUTHORIZATION POLICY

POLICY: Antiseizure Medications – Vigabatrin Prior Authorization Policy
- Sabril® (vigabatrin tablets and powder for solution – Lundbeck, generic)

REVIEW DATE: 09/20/2023

OVERVIEW

Vigabatrin is indicated for the following uses:[1]

- **Infantile spasms**, as monotherapy, in patients 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss. Vigabatrin is not indicated as a first-line agent for complex partial seizures.
- **Refractory complex partial seizures**, as adjunctive therapy, in patients ≥ 2 years of age who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss.

According to the vigabatrin prescribing information, use the lowest dosage and shortest exposure to vigabatrin consistent with clinical objectives.[1] In patients with infantile spasms, vigabatrin should be withdrawn if a substantial clinical benefit is not observed within 2 to 4 weeks. In patients with refractory complex partial seizures, vigabatrin should be withdrawn if a substantial clinical benefit is not observed within 3 months of initiating treatment.

Safety

Vigabatrin has a Boxed Warning with regard to permanent vision loss.[1] In some cases, vigabatrin also can damage the central retina and may decrease visual acuity. The onset of vision loss from vigabatrin is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time after starting treatment, even after months or years. The risk of vision loss increases with increasing dose and cumulative exposure, but there is no dose or exposure known to be free of risk of vision loss. Vision assessment is recommended at baseline (no later than 4 weeks after starting vigabatrin), at least every 3 months during therapy, and about 3 to 6 months after the discontinuation of therapy. Once detected, vision loss due to vigabatrin is not reversible. Because of the risk of vision loss, vigabatrin should be withdrawn from patients with refractory complex partial seizures who fail to show substantial clinical benefit within 3 months of initiation and within 2 to 4 weeks of initiation for patients with infantile spasms, or sooner if treatment failure becomes obvious. Because of the risk of permanent vision loss, vigabatrin is available only through a restricted access program under a Risk Evaluation and Mitigation Strategy (REMS) called the Vigabatrin REMS Program.

Guidelines/Recommendations

In 2012, the American Academy of Neurology (AAN) and the Child Neurology Society updated the evidence-based guideline for the medical treatment of infantile spasms.[2] The guidelines note that low-dose adrenocorticotropic hormone (ACTH) is a first-line agent for the short-term treatment of infantile spasms. ACTH or vigabatrin may be useful for short-term treatment of infantile spasms, with ACTH considered preferentially over vigabatrin. Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to vigabatrin in infants with cryptogenic infantile spasms, to possibly improve developmental outcome. A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin possibly improves long-term developmental outcomes. The Infantile Spasms Working Group (ISWG) published a US consensus report on infantile spasms in 2010.[3] Data regarding ACTH use and vigabatrin use in infantile spasms were detailed. ACTH is an effective first-line therapy for infantile spasms.

Vigabatrin is considered a drug of first choice for infantile spasms with concomitant tuberous sclerosis complex, and it is the drug of second or third choice for children with other symptomatic or cryptogenic infantile spasms.

The AAN and the American Epilepsy Society published a guideline update for treatment-resistant epilepsy (2018) that notes clobazam is probably effective as add-on therapy for LGS and is possibly effective as add-on therapy for treatment-resistant adult focal epilepsy.[4] Vigabatrin is effective as add-on therapy in treatment-resistant adult focal epilepsy based on two Class I studies, but it should not be used as a first-line treatment. The benefits of vigabatrin should be weighed against the risks, particularly the risk of irreversible retinopathy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of vigabatrin. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with vigabatrin as well as the monitoring required for adverse events and long-term efficacy, initial approval requires vigabatrin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of vigabatrin is recommended in those who meet one of the following criteria:

FDA-Approved Indications

15. Infantile Spasms. Approve for 6 months if the patient meets the following (A, B, and C):
- **B)** Patient is ≤ 2 years of age; AND
- **C)** Vigabatrin is being used as monotherapy; AND
- **D)** The medication is prescribed by or in consultation with a neurologist.

16. Treatment-Refractory Complex Partial Seizures. Approve for the duration noted below if the patient meets ONE of the following (A or B):
- **I)** Initial Therapy. Approve for 3 months if the patient meets the following (i, ii, and iii):
  - i. Patient is ≥ 2 years of age; AND
  - ii. Patient has tried and/or is concomitantly receiving at least three other antiseizure medications; AND
    - **4.** Note: Examples of antiseizure medications include valproic acid, gabapentin, phenytoin, carbamazepine, oxcarbazepine, lacosamide, levetiracetam, zonisamide, Fycompa (perampanel tablet or oral suspension), lamotrigine, topiramate, rufinamide, tiagabine, felbamate, Diacomit (stiripentol capsules or oral suspension), and clobazam.
  - iii. The medication is prescribed by or in consultation with a neurologist.
- **J)** Patient is Currently Receiving Vigabatrin. Approve for 1 year if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of vigabatrin is not recommended in the following situations:

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

84. Sabril® tablets and oral solution [prescribing information]. Deerfield, IL: Lundbeck; October 2021.
85. Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: medical treatment of infantile spasms: Report of the guideline development subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2012;78:1974-1980.
86. Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: a US consensus report. *Epilepsia*. 2010;51(10):2175-2189.
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PRIOR AUTHORIZATION POLICY

POLICY: Antiseizure Medications – Ztalmy Prior Authorization Policy
- Ztalmy® (ganaxolone oral suspension – Marinus)

REVIEW DATE: 07/12/2023

OVERVIEW

Ztalmy, a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator, is indicated for the treatment of **seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD)** in patients ≥ 2 years of age.[1]

Disease Overview

CDD is a rare, X-linked developmental epileptic encephalopathy caused by mutations in the CDKL5 gene.[2,3] This disorder can manifest in a broad range of clinical symptoms, including early-onset (< 3 months of age in 90% of patients [median of 5 weeks]), hypotonia, intractable epilepsy, and neurodevelopmental delay impacting cognitive, motor, speech, and visual function. Both cognitive impairment and refractory epilepsy in individuals with CDD are particularly severe; less than 50% of patients have reported a period of seizure freedom > 2 months, with only 12% of patients experiencing seizure freedom for > 12 months. The CDKL5 gene provides instructions for making proteins that are essential for normal brain and neuron development. The CDKL5 protein acts as a kinase, an enzyme that changes the activity of other proteins by adding a phosphate group at specific positions; however, it has not yet been determined which proteins are targeted by the CDKL5 protein. Many cases of CDD have been identified in boys, but because of the location of the gene on the X chromosome, CDD primarily affects girls. Ztalmy is the first antiseizure medication that is FDA-approved for use in CDD and has been prospectively studied.

Clinical Efficacy

The efficacy of Ztalmy in patients with molecularly confirmed CDD was evaluated in one pivotal trial called the Marigold Study (n = 101).[4] Eligible patients were 2 to 21 years of age and had a molecularly confirmed CDKL5 variant that was considered pathogenic or likely to be pathogenic. Patients could remain on a regimen of up to four concomitant antiseizure medications during the trial, including (but not limited to) valproate, levetiracetam, clobazam, and vigabatrin. During the 17-week double-blind phase, the median 28-day major motor seizure frequency was 45.0 in the Ztalmy arm vs. 55.5 in the placebo arm. Compared with the 6-week baseline period, the median percentage change in 28-day major motor seizure frequency was statistically significantly improved (reduced) in the Ztalmy arm vs. the placebo arm (-30.7% vs. -6.9%, respectively; P = 0.0036).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ztalmy. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ztalmy as well as the monitoring required for adverse events and long-term efficacy, approval requires Ztalmy to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ztalmy is recommended in those who meet the following criteria:

FDA-Approved Indication

20. Seizures Associated with Cyclin-Dependent Kinase-Like 5 (CDKL5) Deficiency Disorder. Approve for 1 year if the patient meets the following (A, B, C, and D):
- **A)** Patient is ≥ 2 years of age; AND
- **B)** Patient has a molecularly confirmed pathogenic or likely pathogenic mutation in the CDKL5 gene; AND
- **C)** Patient has tried and/or is concomitantly receiving at least two other antiseizure medications; AND
  Note: This can include any two antiseizure medications, including but not limited to, clobazam, Epidiolex (cannabidiol oral solution), lacosamide, lamotrigine, levetiracetam, phenobarbital, rufinamide, topiramate, valproate, vigabatrin, zonisamide.
- **D)** The medication is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ztalmy is not recommended in the following situations:

18. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Antivirals – Ribavirin (Inhaled Products) Prior Authorization Policy
- Virazole® (ribavirin inhalation solution – Bausch, generic)

REVIEW DATE: 06/07/2023

OVERVIEW

Ribavirin is a synthetic nucleoside with antiviral activity.[1] Ribavirin inhalation solution (referred to as aerosolized ribavirin in this policy) is indicated for the treatment of hospitalized infants and young children with severe lower respiratory tract infections due to **respiratory syncytial virus** (RSV). Treatment early in the course of severe lower respiratory tract infection may be necessary to achieve efficacy.

Disease Overview

RSV causes seasonal annual epidemics worldwide with year-round disease seen in some tropical locations. By 2 years of age, most children have experienced a primary infection; re-infection can occur throughout life.[3] Subsequent infections are usually less severe than a primary infection, particularly among otherwise healthy older children and adults. Recurrent RSV infection manifests as mild upper respiratory tract illness and seldom involves the lower respiratory tract.[2]

Aerosolized ribavirin has also been used off-label in adults for RSV and for other respiratory viral infections, most commonly in immunocompromised patients.[3,4]

Guidelines

The American Academy of Pediatrics (2021) states that no available treatment shortens the course of bronchiolitis or hastens the resolution of RSV symptoms.[2] Management of young children hospitalized with bronchiolitis is supportive. Because of limited evidence for a clinically relevant benefit, potential toxic effects, and high cost, routine use of aerosolized ribavirin is not recommended.

Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice (2019) recommend aerosolized ribavirin in lung transplant recipients with upper or lower respiratory tract infection.[3] Treatment with aerosolized or oral ribavirin for non-solid organ recipients with lower respiratory tract disease can be considered. Aerosolized ribavirin is also a therapeutic option in lung transplant recipients with parainfluenza virus and human metapneumovirus.

The National Comprehensive Cancer Network guidelines for the prevention and treatment of cancer-related infections (version 3.2022 – October 28, 2022) recommend consideration of aerosolized ibavirin for the treatment of lower respiratory tract RSV disease (category 3).[4] Comments related to the recommendation are to limit to patients undergoing stem cell transplant or with leukemia and, that despite limited information in immunocompromised adults with RSV, use should be considered given the potential morbidity and mortality associated with RSV infection.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of aerosolized ribavirin. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with aerosolized ribavirin as well as the monitoring required for adverse events and long-

term efficacy, approval requires aerosolized ribavirin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of aerosolized ribavirin is recommended in those who meet one of the following criteria:

FDA-Approved Indications

21. Respiratory Syncytial Virus (RSV), Treatment. Approve for 1 month if the patient meets the following criteria (A, B, and C):
- **A)** Patient is < 2 years of age; AND
- **B)** Patient is hospitalized; AND
- **C)** The medication is prescribed by or in consultation with a critical care or pulmonary specialist.

Other Uses with Supportive Evidence

2. Respiratory Virus Treatment, Excluding COVID-19. Approve for 1 month if the patient meets the following criteria (A, B, and C):
- **A)** Patient is hospitalized; AND
- **B)** Patient meets ONE of the following criteria (i, ii, or iii):
  - **i.** Patient is a solid organ transplant recipient; OR
  - **ii.** Patient has had a hematopoietic stem cell transplant; OR
  - **iii.** Patient has cancer AND
- **C)** The medication is prescribed by or in consultation with a critical care specialist, transplant physician, oncologist, infectious diseases physician, or pulmonologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of aerosolized ribavirin is not recommended in the following situations:

19. COVID-19 (Coronavirus Disease 2019). Data are preliminary, additional study is needed.[5,6] A Phase I, open-label, non-US (Greece, Brazil, and Mexico), non-randomized, two-arm study was conducted to evaluate the safety and efficacy of aerosolized ribavirin (as Virazole) in hospitalized adults with significant respiratory distress due to COVID-19 (n = 51).[5] Patients received aerosolized ribavirin (100mg/mL for 30min or 50mg/mL for 60min) twice daily for up to 6 days. Improvement of one or more level in clinical status severity was observed in 31.4% (n = 16/51) and 78.4% (n = 40/51) of patients at end-of-treatment and day 30, respectively. Of 21 patients who required a ventilator, 16 (76.2%) were able to discontinue ventilator use. One case series reported on five hospitalized adults with COVID-19 who received aerosolized ribavirin (100 mg/mL twice daily for 6 days) solution as part of a compassionate use program in Italy (patients were also managed in accordance with Italian treatment guidelines for COVID).[6] All patients fully recovered. Ribavirin is not addressed as a recommended treatment modality in guidelines from the Infectious Diseases Society of America or the National Institutes of Health.[7,8]

20. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Antivirals – Ribavirin (Oral Products) Prior Authorization Policy
- ribavirin tablets (generic)
- ribavirin capsules (generic)

REVIEW DATE: 06/14/2023

OVERVIEW

The ribavirin products included in this Prior Authorization policy are indicated for use **in combination with pegylated interferons or interferon for the treatment of chronic HCV** in adults and children with compensated disease. Ribavirin remains a component of some regimens for the management of HCV; however, there is no role for interferon (specifically non-pegylated interferon) in the management of HCV.[2] The specific indications vary slightly among the oral ribavirin products:

- Ribavirin capsules are indicated in combination with PegIntron® (peginterferon alfa-2b injection) or Intron A® (interferon alfa-2b injection) for the treatment of chronic HCV in patients ≥ 3 years of age with compensated liver disease.[1]
- Ribavirin tablets are indicated in combination with Pegasys® (peginterferon alfa-2a) for the treatment of patients ≥ 5 years of age with chronic HCV with compensated liver disease who have not previously been treated with interferon alfa.[7]

Ribavirin is an antiviral agent with direct antiviral activity in tissue culture against many RNA viruses.[1] Ribavirin increases the mutation frequency in the genomes of several viruses and ribavirin triphosphate inhibits hepatitis C virus (HCV) polymerase in a biochemical reaction.

According to the Centers for Disease Control and Prevention, oral ribavirin has been used off-label to treat other systemic viral infections including, but not limited to, Lassa fever[5,6], Nipah virus[13], West Nile virus[14], and Crimean Congo hemorrhagic fever.[4,12] In addition, oral ribavirin has a place in therapy for the management of respiratory syncytial virus in transplant recipients.[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of ribavirin. The intent of this Prior Authorization program is to ensure ribavirin is not used in the absence of pegylated interferon or a direct-acting antiviral for the treatment of hepatitis C virus (HCV). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients being treated with ribavirin, as well as the monitoring required for adverse events and efficacy, approval requires ribavirin (for hepatitis C indications) to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: Automation is in place for the use of a pegylated interferon or a direct-acting antiviral for hepatitis C virus (HCV) in the past 130 days. This is used as a surrogate marker for HCV. If the criteria for prior use of a pegylated interferon or direct-acting antiviral for HCV are not met at the point-of-service, coverage will be determined by Prior Authorization criteria.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of ribavirin is recommended in those who meet one of the following criteria:

FDA-Approved Indication

22. Hepatitis C Virus (HCV). Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient meets ONE of the following criteria (i or ii):
  - **i.** The medication is prescribed in combination with peginterferon alfa; OR
    Note: Pegasys (pegylated interferon alfa-2a injection) is an example of a peginterferon alfa.
  - **ii.** The medication is prescribed in combination with a direct-acting antiviral for HCV; AND
    Note: Examples of direct-acting antivirals for HCV are Epclusa (velpatasvir/sofosbuvir tablets), Sovaldi (sofosbuvir tablets/oral pellets), Harvoni (ledipasvir/sofosbuvir tablets/oral pellets), Viekira Pak (paritaprevir/ombitasvir/ritonavir tablets + dasabuvir tablets, co-packaged), Zepatier (elbasvir/grazoprevir tablets).
- **B)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, liver transplant physician, or infectious diseases physician.

Other Uses with Supportive Evidence

23. Other Systemic Viral Infections, Excluding COVID-19 (Coronavirus Disease 2019). Approve for 1 year.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of ribavirin is not recommended in the following situations:

21. COVID-19 (Coronavirus Disease 2019). Efficacy is not established.[8,9] Ribavirin is not addressed as a treatment modality in guidelines from the Infectious Diseases Society of America or the National Institutes of Health.[10,11]

22. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Attention Deficit Hyperactivity Disorder Non-Stimulant Medications Prior Authorization Policy

- Intuniv® (guanfacine extended-release tablets – Shire, generic)
- Kapvay® (clonidine hydrochloride extended-release tablets – Concordia, generic)
- Strattera® (atomoxetine capsules – Eli Lilly, generic)
- Qelbree® (viloxazine extended-release capsules – Supernus)

REVIEW DATE: 07/26/2023

OVERVIEW

Atomoxetine capsules (Strattera, generic), guanfacine extended-release (ER) tablets (Intuniv, generic), clonidine ER tablets (Kapvay, generic), and Qelbree are non-stimulant medications approved for the **treatment of attention deficit hyperactivity disorder** (ADHD).[1-4]

Atomoxetine capsules, a selective norepinephrine reuptake inhibitor, and Qelbree, a selective norepinephrine reuptake inhibitor, are indicated for the treatment of ADHD in children ≥ 6 years of age, adolescents, and adults.[1,4] Guanfacine ER tablets and clonidine ER tablets, both alpha agonists, are approved for use in children and adolescents 6 to 17 years of age with ADHD.[2,3] Guanfacine ER tablets and clonidine ER tablets are indicated for use as monotherapy or as adjunctive therapy to stimulant medications.

Clinical Efficacy

Patients with pervasive developmental disorders who have symptoms of ADHD respond to ADHD medications at a reduced rate compared with typically developing peers and often with undesirable side effects.[5,6] However, there is evidence to support use of these agents (e.g., stimulants, atomoxetine capsules, guanfacine ER tablets, and clonidine ER tablets) in this patient population.

POLICY STATEMENT

5. Prior Authorization is recommended for prescription benefit coverage of atomoxetine capsules (Strattera, generic), clonidine ER tablets (Kapvay, generic), guanfacine ER tablets (Intuniv, generic), and Qelbree. All approvals are provided for the duration noted below.

Automation: An age edit is in place such that a patient 6 to 18 years of age will be approved at the point of service. For a patient < 6 or > 18 years of age, coverage will be determined by Prior Authorization criteria.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of atomoxetine capsules (Strattera, generic), clonidine ER tablets (Kapvay, generic), or guanfacine ER tablets (Intuniv, generic) is recommended in those who meet one of the following criteria:

FDA-Approved Indication

7. **Attention Deficit Hyperactivity Disorder.** Approve for 1 year if the patient is ≥ 6 years of age.

Other Uses with Supportive Evidence

8. **Pervasive Developmental Disorders (e.g., autism spectrum disorder, Asperger's disorder).** Approve for 1 year if the patient has symptoms of attention deficit hyperactivity disorder (e.g., inattention, hyperactivity).

II. Coverage of Qelbree is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Attention Deficit Hyperactivity Disorder.** Approve for 1 year if the patient is ≥ 6 years of age.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of atomoxetine capsules (Strattera, generic), clonidine ER tablets (Kapvay, generic), guanfacine ER tablets (Intuniv, generic), or Qelbree is not recommended in the following situations:

18. **Binge-Eating Disorder.** In one 10-week, placebo-controlled study in outpatients with binge-eating disorder (n = 40), atomoxetine was associated with a significantly greater reduction in binge-eating episode frequency vs. placebo.[7] Additional studies with atomoxetine are needed. There are no data with guanfacine ER tablets, clonidine ER tablets, or Qelbree.

19. **Depression without Attention Deficit/Hyperactivity Disorder.** Limited information is available on the use of atomoxetine for the treatment of major depressive disorder. In three case reports and one case series in 15 patients with depressive disorders, adding atomoxetine to a selective serotonin reuptake inhibitor resulted in further improvement.[8,9] However, in a published controlled trial, patients with major depressive disorder (without ADHD) [n =276] were treated with sertraline at doses up to 200 mg/day.[10] Patients who continued to experience depressive symptoms (n = 146) were then randomly assigned to either treatment with atomoxetine 40 to 120 mg/day or placebo for an additional 8 weeks. There was no difference between the atomoxetine/sertraline and placebo/sertraline treatment groups in mean change in depressive symptom severity or in the number of patients whose depressive symptoms remitted (40.3% vs. 37.8%, respectively; P = 0.865). Atomoxetine did not improve clinically significant depression in patients with Parkinson disease (n = 55) in one study.[11] There are no data with guanfacine ER tablets, clonidine ER tablets, or Qelbree.

D)

20. **Fibromyalgia.** In case reports, atomoxetine was effective in reducing fatigue and pain in fibromyalgia syndrome.[12] Well-controlled trials with atomoxetine are needed to establish safety and efficacy. There are no data with guanfacine ER tablets, clonidine ER tablets, or Qelbree.

21. **Improve Cognitive Function (or Neuroenhancement).** The use of prescription medication to augment cognitive or affective function in otherwise healthy individuals (also known as neuroenhancement) is increasing in adult and pediatric populations.[20] A 2013 Ethics, Law, and Humanities Committee position paper, endorsed by the American Academy of Neurology, indicates that based on currently available data and the balance of ethics issues, neuroenhancement in children and adolescents without a diagnosis of a neurologic disorder is not justifiable. The prescription of neuroenhancements is inadvisable due to numerous social, developmental, and professional integrity

issues. Several studies have evaluated atomoxetine for cognitive function in various patient populations, including patients with Huntington disease[12], Alzheimer's disease[14], schizophrenia[15,16], and Parkinson's disease.[17] However, atomoxetine has not demonstrated clinical benefit.

22. **Long-Term Combination Therapy (i.e., > 2 months) with atomoxetine (Strattera, generic) and Central Nervous System (CNS) Stimulants used for the Treatment of Attention Deficit/Hyperactivity Disorder (e.g., mixed amphetamine salts ER capsules [Adderall XR, generic], methylphenidate ER tablets, methylphenidate immediate-release tablets).** Currently, data do not support using atomoxetine and CNS stimulant medications concomitantly.[18,19] Short-term drug therapy (2 months or less) with both atomoxetine and CNS stimulant medications is allowed for transitioning the patient to only one drug. Guanfacine ER tablets and clonidine ER tablets are indicated for use as monotherapy or as adjunctive therapy to CNS stimulant medications; therefore, long-term combination therapy with either agent and CNS stimulants is appropriate.[2-3] Qelbree labeling does not address combination use with CNS stimulants at this time.[4]

23. **Nocturnal Enuresis.** In case reports, children with ADHD and other comorbid psychiatric diagnoses who had nocturnal enuresis and were treated with atomoxetine had resolution of their enuresis.[21] In one controlled trial in pediatric patients (n = 87) with nocturnal enuresis, atomoxetine increased the average number of dry nights per week by 1.47 vs. 0.60 for placebo (P = 0.01).[22] Additional controlled trials with atomoxetine are needed. Data with guanfacine ER tablets, clonidine ER tablets, or Qelbree are lacking.

E)

24. **Weight Loss.** In one 12-week, placebo-controlled study in obese women (n = 30), atomoxetine resulted in a mean -3.7% loss vs. 0.2% gain with placebo when combined with a hypocaloric diet (500 kcal/day deficit).[23] Atomoxetine did not demonstrate efficacy for weight reduction in patients with schizophrenia (n = 37) treated with antipsychotics (clozapine or olanzapine).[24] Additional studies are needed.

25. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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6.

PRIOR AUTHORIZATION POLICY

POLICY: Attention Deficit Hyperactivity Disorder Stimulant Medications Prior Authorization Policy

REVIEW DATE: 07/26/2023

OVERVIEW

The central nervous system (CNS) stimulant medications in this policy are indicated for the following uses:[1-24,43,44,48-54]

- **Attention deficit hyperactivity disorder (ADHD)**, treatment. All of the stimulant medications in this policy are indicated for the treatment of ADHD.
- **Binge eating disorder**, treatment. Vyvanse is the only stimulant medication indicated for the treatment of binge eating disorder.
- **Narcolepsy**, treatment. Several methylphenidate and amphetamine-containing products are also indicated for the treatment of narcolepsy.
- **Exogenous obesity**, treatment. Evekeo is indicated as adjunctive therapy for the short-term (i.e., a few weeks) treatment of exogenous obesity.

Dextroamphetamine sulfate tablets, Zenzedi, and Adderall (generic) are indicated in patients ≥ 3 years of age; the other products are indicated in patients ≥ 6 years of age, except for Mydayis which is indicated in patients ≥ 13 years of age.[1,2,6,19,43] Adderall XR (generic), Adzenys ER, Adzenys XR-ODT, Concerta (generic), Mydayis, Vyvanse, Xelstrym, and several methylphenidate products are indicated for use in adults with ADHD.[2,5,9,24,43,48,54] Jornay PM is the only stimulant taken in the evening.[49]

Other Uses with Supportive Evidence

Idiopathic hypersomnia: A condition similar to narcolepsy, idiopathic hypersomnia is characterized by constant or recurrent daytime sleepiness with no other cause of sleepiness, prolonged nocturnal sleep, difficulty awakening with sleep drunkenness, and long unrefreshing naps with no of cataplexy.[29-32]

Guidelines

Narcolepsy and other hypersomnias: The practice parameters from the American Academy of Sleep Medicine for the treatment of central disorders of hypersomnolence (2021) state that dextroamphetamine and methylphenidate, in addition to other wakefulness-promoting agents, are effective for treatment of daytime sleepiness due to narcolepsy.[25] The parameters also state that methylphenidate, in addition to other agents, may be effective for the treatment of daytime sleepiness due to idiopathic hypersomnia. As there may be underlying causes/behaviors associated with excessive daytime sleepiness, a sleep specialist physician has the training to correctly recognize and diagnose this condition.

Major depressive disorder (MDD): The 2010 American Psychiatric Association practice guidelines for the treatment of patients with MDD state that many clinicians find augmentation of antidepressants with low doses of stimulants such as methylphenidate or dextroamphetamine may help ameliorate otherwise suboptimally responsive depression, although not all clinical trials have shown benefits from this strategy.[26] There are no clear guidelines regarding the length of time stimulants should be co-administered. A 16-week randomized, double-blind, placebo-controlled trial in older outpatients with major depression (mean age of 70 years) [n = 143] found that combined treatment with citalopram and methylphenidate demonstrated an enhanced clinical response profile in mood and wellbeing, as well as a higher rate of remission, compared with either drug alone.[45]

Cancer-related fatigue: The National Comprehensive Cancer Network (NCCN) guidelines on cancer-related fatigue (version 2.2023 – January 30, 2023) state to consider use of psychostimulants (i.e., methylphenidate) in consideration of other modifiable causes.[27] The NCCN guidelines on adult cancer pain (version 1.2023 – March 7, 2023) state that sedation may hinder the achievement of dose titration of opioids to levels that provide adequate analgesia.[28] If opioid-induced sedation develops, it may be managed by administration of a psychostimulant, such as methylphenidate, dextroamphetamine, modafinil, armodafinil, or by adding caffeine. A meta-analysis of treatments for fatigue associated with palliative care showed a

superior effect for methylphenidate in cancer-related fatigue.[46] A review of methylphenidate for cancer-related fatigue found a small but significant improvement in fatigue over placebo (P = 0.005).[47]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of ADHD stimulant medications in adults. Only patients ≥ 18 years of age will be required to meet the Prior Authorization criteria below. All approvals are provided for the duration noted below.

Automation: An age edit is in place such that a patient less than 18 years of age will be approved at the point of service. For a patient ≥ 18 years of age, coverage will be determined by Prior Authorization criteria.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of ADHD stimulant medications is recommended in those who meet one of the following criteria:

FDA-Approved Indications

9. **Attention Deficit Hyperactivity Disorder.** Approve for 1 year.

2. **Binge Eating Disorder.** Approve only Vyvanse for 1 year if the patient is ≥ 18 years of age.

3. **Narcolepsy.** Approve for 1 year.

Other Uses with Supportive Evidence

4. **Depression, Adjunctive/Augmentation Treatment in an Adult.** Approve for 1 year if the patient is concurrently receiving other medication therapy for depression.
   Note: Examples of medications for the treatment of depression include selective serotonin reuptake inhibitors.

5. **Fatigue associated with Cancer and/or its Treatment.** Approve for 1 year.

6. **Idiopathic Hypersomnolence.** Approve for 1 year if the diagnosis is confirmed by a sleep specialist physician or at an institution that specializes in sleep disorders (i.e., sleep center).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of ADHD stimulant medications is not recommended in the following situations:

1. **Fatigue Associated with Multiple Sclerosis.** There are no published studies supporting this use. In addition, neither recent review articles nor the 2021 practice parameters for the treatment of narcolepsy and other hypersomnias of central origin mention stimulants (only modafinil). Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin, updated in 2021, state that modafinil may be effective for the treatment of daytime sleepiness due to multiple sclerosis.[25] Agents that have been studied for the treatment of fatigue due to multiple sclerosis include amantadine, modafinil, and methylphenidate; these medications were not superior to placebo for this use.[41]

26. **Long-Term Combination Therapy (i.e., > 2 months) with atomoxetine capsules (Strattera®, generic) and Central Nervous System (CNS) Stimulants for the treatment of Attention Deficit/Hyperactivity Disorder (e.g., mixed amphetamine salts extended-release capsules [Adderall XR®, generics], methylphenidate extended-release tablets, methylphenidate immediate-release tablets).** Currently, data do not support using Strattera and CNS stimulant medications concomitantly.[42] Short-term drug therapy (≤ 2 months) with both atomoxetine and CNS stimulant medications is allowed for transitioning the patient to only one drug. Guanfacine extended-release tablets (Intuniv®, generic) and clonidine extended-release tablets (Kapvay®, generic) are indicated for use as monotherapy, or as adjunctive therapy to CNS stimulant medications; therefore, long-term combination therapy with either agent and CNS stimulants is appropriate.[33,34]

27. **Neuroenhancement.** The use of prescription medication to augment cognitive or affective function in otherwise healthy individuals (also known as neuroenhancement) is increasing in adult and pediatric populations.[35] A 2013 Ethics, Law, and Humanities Committee position paper, endorsed by the American Academy of Neurology indicates that based on available data and the balance of ethics issues, neuroenhancement in legally and developmentally non-autonomous children and adolescents without a diagnosis of a neurologic disorder is not justifiable. In nearly autonomous adolescents, the fiduciary obligation of the physician may be weaker, but the prescription of neuroenhancements is inadvisable due to numerous social, developmental, and professional integrity issues.

28. **Weight Loss.** Of the CNS stimulants, only amphetamine sulfate tablets (e.g., Evekeo tablets) are indicated for exogenous obesity, as a short-term (i.e., a few weeks) adjunct in a regimen of weight reduction based on caloric restriction, for patients in whom obesity is refractory to alternative therapy (e.g., repeated diets, group programs, and other drugs).[20] However, guidelines on the management of obesity do not address or recommend use of amphetamine (or any other CNS stimulants).[36-40]

29. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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53. Azstarys™ capsules [prescribing information]. Grand Rapids, MI: Corium; March 2021.
54. Xelstrym™ transdermal system [prescribing information. Miami, FL: Noven; March 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Benign Prostatic Hyperplasia – Entadfi Prior Authorization Policy
- Entadfi™ (finasteride and tadalafil capsules – Veru)

REVIEW DATE: 11/29/2023

OVERVIEW

Entadfi, a combination of finasteride 5 mg (a 5-alpha-reductase inhibitor) and tadalafil 5 mg (a phosphodiesterase 5 inhibitor), is indicated to initiate treatment of the signs and symptoms of **benign prostatic hyperplasia** in men with an enlarged prostate for up to 26 weeks.[1]

Entadfi has a limitation of use which states the medication is not recommended for more than 26 weeks because the incremental benefit of tadalafil decreases from 4 weeks until 26 weeks, and then the incremental benefit beyond 26 weeks is unknown.[1] This is the same limitation of use included in tadalafil labeling and it applies to situations in which tadalafil is used with finasteride to initiate benign prostatic hyperplasia treatment.[2]

Guidelines

The American Urological Association guidelines on the management of lower urinary tract symptoms attributed to benign prostatic hyperplasia (2023) note that 5-alpha reductase inhibitors (alone or in combination with an alpha blocker) are recommended as a treatment option to prevent progression of lower urinary tract symptoms/benign prostatic hyperplasia.[3] Guidelines note that clinicians may offer the combination of low-dose 5 mg tadalafil with an alpha blocker, however, there is little benefit with the combination. Regarding tadalafil, it is noted that in patients with benign prostatic hyperplasia, irrespective of a comorbid erectile dysfunction, daily 5 mg tadalafil should be discussed as a treatment option.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Entadfi. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Entadfi is recommended in those who meet the following criteria:

FDA-Approved Indication

24. Benign Prostatic Hyperplasia. Approve for 6 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Entadfi is not recommended in the following situations:

23. Erectile Dysfunction without Benign Prostatic Hyperplasia. Entadfi is not indicated for erectile dysfunction in patient without benign prostatic hyperplasia.[1]

24. Alopecia. Entadfi is not indicated for alopecia.[1] Finasteride 1 mg tablets are indicated for the treatment of male pattern hair loss (androgenetic alopecia).[4]

25. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Bone Modifiers – Evenity Prior Authorization Policy
- Evenity® (romosozumab-aqqg subcutaneous injection – Amgen)

REVIEW DATE: 05/24/2023

OVERVIEW

Evenity, a sclerostin inhibitor, is indicated for the treatment of **osteoporosis** in postmenopausal women at high risk for fracture, defined as a of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.[1] It is recommended to adequately supplement with calcium and vitamin D during treatment with Evenity. According to the Evenity prescribing information, the anabolic effect of Evenity wanes after 12 monthly doses of therapy. Therefore, limit the duration of use to 12 monthly doses. If osteoporosis therapy remains warranted, continued therapy with an anti-resorptive therapy (e.g., alendronate) should be considered.

Guidelines

Evenity is cited guidelines that discusses the management of postmenopausal osteoporosis.[2,3]

- **Postmenopausal Osteoporosis:** The Endocrine Society (2020) issued a guideline update regarding the pharmacological management of osteoporosis in postmenopausal women which addressed Evenity.[2] In postmenopausal women with osteoporosis at very high risk of fractures such as patients with severe osteoporosis (i.e., low T-score < -2.5 and fractures) or multiple fractures, Evenity therapy is recommended for up to 1 year for the reduction of vertebral, hip, and nonvertebral fractures. The recommended dose is 210 mg monthly by subcutaneous injection for 12 months. In postmenopausal women with osteoporosis who have completed a course of Evenity, antiresorptive osteoporosis therapy is recommended to maintain bone density gains and reduce fracture risk.
- **Treatment and Prevention of Osteoporosis:** In 2022, the Bone Health and Osteoporosis Foundation updated a guideline for the prevention and treatment of osteoporosis (2022).[3] In the 12-month FRAME trial involving women with postmenopausal osteoporosis, Evenity, compared with placebo, reduced the risk of new vertebral fracture by 73% and clinical fractures by 36%. In the ARCH trial, high-risk postmenopausal women experienced significantly fewer fractures when given Evenity compared with alendronate for 12 months (48% fewer new vertebral fractures, 19% fewer non-vertebral fractures, and 38% fewer hip fractures). However, the Boxed Warning that Evenity has regarding an increased risk for myocardial infarction, stroke, and cardiovascular death was concerning.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Evenity. Coverage is limited to 12 monthly doses during the therapy course.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Evenity is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Osteoporosis Treatment of a Postmenopausal Patient.** Approve for 1 year if the patient meets ALL of the following criteria (A, B, and C):
   - **A)** Patient meets ONE of the following conditions (i, ii, or iii):
     - **i.** Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip and/or 33% (one-third) radius (wrist); OR
     - **ii.** Patient has had an osteoporotic fracture or a fragility fracture; OR
     - **iii.** Patient meets both of the following (a and b):
       - **a)** Patient has low bone mass; AND
         Note: Examples of a low bone mass include a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one third) radius (wrist).
       - **b)** According to the prescriber, the patient is at high risk for fracture; AND
   - **B)** The patient meets ONE of the following (i, ii, iii, or iv):
     - **i.** Patient has tried ibandronate injection (Boniva IV) or zoledronic acid injection (Reclast); OR
     - **ii.** Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a or b):
       Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).
       - **a)** According to the prescriber, the patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR
         Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.
       - **b)** Patient has experienced significant intolerance to an oral bisphosphonate; OR
         Note: Examples of significant intolerance include severe gastrointestinal related adverse events, severe musculoskeletal related adverse events, or a femoral fracture.
     - **iii.** Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):
       - **a)** Patient cannot swallow or has difficulty swallowing; OR
       - **b)** Patient cannot remain in an upright position post oral bisphosphonate administration; OR
       - **c)** Patient has a pre-existing gastrointestinal medical condition; OR
         Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).
     - **iv.** Patient meets one of the following conditions (a, b, or c):
       - **a)** Severe renal impairment; OR
         Note: An example of severe renal impairment is a creatinine clearance < 35 mL/min.
       - **b)** Chronic kidney disease; OR
       - **c)** Patient has had an osteoporotic fracture or a fragility fracture; AND
   - **C)** Patient has received no more than 12 monthly doses during this therapy course.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Evenity is not recommended in the following situations:

30. Osteoporosis Prevention. Evenity is not indicated for the prevention of osteoporosis.

31. Concurrent Use with Other Medications for Osteoporosis.
Note: Examples of medications for osteoporosis that Evenity should not be given with include oral bisphosphonates (e.g., alendronate, risedronate, ibandronate), intravenous bisphosphonates (zoledronic acid injection [Reclast], intravenous ibandronate), Prolia (denosumab subcutaneous injection), Forteo (teriparatide subcutaneous injection, generic), Tymlos (abaloparatide subcutaneous injection), and calcitonin nasal spray (Miacalcin/Fortical). However, this does NOT exclude use of calcium and/or vitamin D supplements in combination with Evenity.

32. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Bone Modifiers – Ibandronate Intravenous Prior Authorization Policy
- Boniva® (ibandronate intravenous infusion – Genentech/Roche, generic)

REVIEW DATE: 03/22/2023

OVERVIEW
Ibandronate injection is indicated for the treatment of **osteoporosis** in postmenopausal women.[1]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of ibandronate injection. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of ibandronate injection is recommended in those who meet the following criteria:

FDA-Approved Indication

2. Osteoporosis – Treatment for a Postmenopausal Patient. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient meets ONE of the following conditions (i, ii, or iii):
- **iv.** Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip and/or 33% (one-third) radius (wrist); OR
- **v.** Patient has had an osteoporotic fracture or a fragility fracture; OR
- **vi.** Patient meets both of the following (a and b):
  - **a)** Patient has low bone mass; AND
    Note: An example of low bone mass includes a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip and/or 33% (one-third) radius (wrist).
  - **b)** According to the prescriber, patient is at high risk for fracture; AND
- **B)** Patient meets ONE of the following (i, ii, iii, or iv):
- **i.** Patient has tried ibandronate injection (Boniva) or zoledronic acid injection (Reclast); OR
- **ii.** Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a or b):
  Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).
  - **a)** According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR
    Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.
  - **b)** Patient has experienced significant intolerance to an oral bisphosphonate; OR

Note: Examples of significant intolerance include severe gastrointestinal related adverse events, severe musculoskeletal related adverse events, or a femoral fracture.

iii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):

a) Patient cannot swallow or has difficulty swallowing; OR

b) Patient cannot remain in an upright position post oral bisphosphonate administration; OR

c) Patient has a pre-existing gastrointestinal medical condition in which intravenous bisphosphonate therapy may be warranted; OR

Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

iv. Patient has had an osteoporotic fracture or a fragility fracture.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of ibandronate injection is not recommended in the following situations:

33. Osteoporosis Prevention. Ibandronate injection is not indicated for the prevention of osteoporosis and supporting data are limited.

34. Concurrent Use of Ibandronate Injection with Other Medications for Osteoporosis.
Note: Examples of medications for osteoporosis that ibandronate injection should not be given with include oral bisphosphonates (e.g., alendronate, risedronate, ibandronate), other intravenous bisphosphonates (e.g., zoledronic acid injection [Reclast]), Prolia (denosumab subcutaneous injection), Evenity (romosozumab-aqqg subcutaneous injection), Forteo (teriparatide subcutaneous injection), Tymlos (abaloparatide subcutaneous injection), and calcitonin nasal spray. However, this does NOT exclude use of calcium and/or vitamin D supplements in combination with ibandronate injection.

35. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Bone Modifiers – Prolia Prior Authorization Policy
- Prolia® (denosumab subcutaneous injection – Amgen)

REVIEW DATE: 09/27/2023

OVERVIEW

Prolia, a receptor activator of nuclear factor kappa-B ligand inhibitor, is indicated for the following uses:[1]

- **Bone loss (treatment to increase bone mass), in men with nonmetastatic prostate cancer** at high risk for fracture receiving androgen deprivation therapy.
- **Bone loss (treatment to increase bone mass), in women with breast cancer** at high risk for fracture receiving adjuvant aromatase inhibitor therapy.
- **Glucocorticoid-induced osteoporosis** (treatment), in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months.
- **Osteoporosis**, treatment of **postmenopausal women** at high risk of fracture.
- **Osteoporosis**, treatment to **increase bone mass in men** at high risk for fracture.

In general, high risk of fractures is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.[1] Of note, denosumab subcutaneous injection is also available under the brand name Xgeva®, and is indicated for the prevention of skeletal-related events in patients with multiple myeloma, as well as in patients with bone metastases from solid tumors, giant cell tumor of bone, and hypercalcemia of malignancy.[2]

Dosing Information

For all indications, the dose is 60 mg once every 6 months as a subcutaneous injection.[1]

Guidelines

Several guidelines address Prolia.

- **Breast Cancer/Prostate Cancer:** The National Comprehensive Cancer Network guidelines for breast cancer (version 4.2023 – March 23, 2023)[6] and prostate cancer (version 4.2023 – September 7, 2023)[7] note that if patients are receiving agents that impact bone mineral density (BMD), bisphosphonates (oral/intravenous), as well as Prolia, should be considered to maintain or improve BMD and/or reduce the risk of fractures.
- **Glucocorticoid-Induced Osteoporosis (GIO):** In 2017, the American College of Rheumatology updated guidelines for the prevention and treatment of GIO.[5] In various clinical scenarios, oral bisphosphonates are preferred, followed by intravenous bisphosphonates (e.g., zoledronic acid intravenous infusion [Reclast]).
- **Postmenopausal Osteoporosis:** Prolia is prominently featured in guidelines for postmenopausal osteoporosis by the Endocrine Society (2019)[3] and the American Association of Clinical Endocrinologists and the American College of Endocrinology (2020).[4] Prolia is one of several agents cited as an alternative for patients at high risk for fractures. The Bone Health and Osteoporosis Foundation clinician's guide for prevention and treatment of osteoporosis (2022) cites Prolia as robustly reducing vertebral and non-vertebral fractures in studies involving women with postmenopausal osteoporosis.[8]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Prolia. All approvals are provided for 1 year in duration. In the approval indication, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Automation: Smart Coverage Review uses patient claim history to answer Prior Authorization questions regarding medication history of Boniva® (ibandronate intravenous infusion) or Reclast® (zoledronic acid intravenous infusion). A 2-year look back period will be used to check claim history and automate for use of either agent (Boniva intravenous or Reclast). If not in claims, medication can be obtained through Prior Authorization criteria. For all reviews, other Prior Authorization criteria listed below will also be applied.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Prolia is recommended in those who meet one of the following criteria:

FDA-Approved Indications

16. **Bone Loss (Treatment to Increase Bone Mass) in Patients with Breast Cancer at High Risk for Fracture Receiving Adjuvant Aromatase Inhibitor Therapy.** Approve for 1 year if the patient meets the following (A and B):
    - **A)** Patient has breast cancer that is not metastatic to bone; AND
    - **B)** Patient is receiving aromatase inhibitor therapy.
      Note: Examples of aromatase inhibitor therapy are anastrozole, letrozole, or exemestane.

17. **Bone Loss (Treatment to Increase Bone Mass) in Patients with Nonmetastatic Prostate Cancer at High Risk for Fracture Receiving Androgen Deprivation Therapy.** Approve for 1 year if the patient meets the following (A and B):
    - **A)** Patient has prostate cancer that is not metastatic to bone; AND
    - **B)** Patient meets ONE of the following conditions (i or ii):
      - **i.** Patient is receiving androgen deprivation therapy; OR
        Note: Examples of androgen deprivation therapy are Lupron Depot (leuprolide depot suspension injection), Eligard (leuprolide acetate suspension injectable), Trelstar (triptorelin pamoate suspension injection), and Zoladex (goserelin implant).
      - **ii.** Patient has undergone bilateral orchiectomy.

18. **Glucocorticoid-Induced Osteoporosis – Treatment.** Approve for 1 year if the patient meets the following (A and B):
    - **A)** Patient is either initiating or continuing systemic glucocorticoids; AND
      Note: An example of a systemic glucocorticoid is prednisone.
    - **B)** Patient meets ONE of the following (i, ii, iii, or iv):
      - **i.** Patient has tried zoledronic acid intravenous infusion (Reclast); OR
      - **ii.** Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a or b):
        Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).
        - **a)** According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR

Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.

b) Patient has experienced significant intolerance to an oral bisphosphonate; OR
Note: Examples of significant intolerance include severe gastrointestinal related adverse events and/or severe musculoskeletal related adverse events.

iii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):
- **a)** Patient cannot swallow or has difficulty swallowing; OR
- **b)** Patient cannot remain in an upright position post oral bisphosphonate administration; OR
- **c)** Patient has a pre-existing gastrointestinal medical condition; OR
  Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

iv. Patient meets one of the following conditions (a, b, or c):
- **a)** Severe renal impairment; OR
  Note: An example of severe renal impairment is a creatinine clearance < 35 mL/min.
- **b)** Chronic kidney disease; OR
- **c)** Patient has had an osteoporotic fracture or a fragility fracture.

~~19.~~ **Osteoporosis Treatment for a Postmenopausal Patient.** Approve for 1 year if the patient meets the following (A and B):

A) Patient meets ONE of the following conditions (i, ii, or iii):
- **i.** Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist); OR
- **ii.** Patient has had an osteoporotic fracture or a fragility fracture; OR
- **iii.** Patient meets both of the following (a and b):
  - **a)** Patient has low bone mass; AND
    Note: An example of low bone mass includes a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist).
  - **b)** According to the prescriber, patient is at high risk for fracture; AND

B) Patient meets ONE of the following (i, ii, iii, or iv):
- **i.** Patient has tried ibandronate intravenous injection (Boniva) or zoledronic acid intravenous infusion (Reclast); OR
- **ii.** Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a or b):
  Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).

a) According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR
Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.

b) Patient has experienced significant intolerance to an oral bisphosphonate; OR
Note: Examples of significant intolerance include severe gastrointestinal related adverse events and/or severe musculoskeletal related adverse events.

iii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):

a) Patient cannot swallow or has difficulty swallowing; OR
b) Patient cannot remain in an upright position post oral bisphosphonate administration; OR
c) Patient has a pre-existing gastrointestinal medical condition; OR
Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

iv. Patient meets one of the following conditions (a, b, or c):
a) Severe renal impairment; OR
Note: An example of severe renal impairment is a creatinine clearance < 35 mL/min.
b) Chronic kidney disease; OR
c) Patient has had an osteoporotic fracture or a fragility fracture.

20. Osteoporosis Treatment (to Increase Bone Mass) for Men*. Approve for 1 year if the patient meets the following (A and B):

A) Patient meets ONE of the following conditions (i, ii, or iii):
i. Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist); OR
ii. Patient has had an osteoporotic fracture or a fragility fracture; OR
iii. Patient meets both of the following (a and b):
a) Patient has low bone mass; AND
Note: An example of low bone mass includes a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist).
b) According to the prescriber, patient is at high risk of fracture; AND

B) Patient meets ONE of the following (i, ii, iii, or iv):
i. Patient has tried zoledronic acid intravenous infusion (Reclast); OR
ii. Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a or b):
Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).
a) According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR
Note: Example of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.
b) Patient has experienced significant intolerance to an oral bisphosphonate; OR
Note: Examples of significant intolerance include severe gastrointestinal related adverse events and/or severe musculoskeletal related adverse events.

iii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):
a) Patient cannot swallow or has difficulty swallowing; OR
b) Patient cannot remain in an upright position post oral bisphosphonate administration; OR
c) Patient has a pre-existing gastrointestinal medical condition; OR
Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

iv. Patient meets one of the following conditions (a, b, or c):
a) Severe renal impairment; OR
Note: An example of severe renal impairment is a creatinine clearance < 35 mL/min.

b) Chronic kidney disease (CKD); OR
c) Patient has had an osteoporotic fracture or a fragility fracture.

* Refer to the Policy Statement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Prolia is not recommended in the following situations:

36. Concurrent Use with Other Medications for Osteoporosis.
Note: Examples of medications for osteoporosis that Prolia should not be given with include teriparatide subcutaneous injection (Forteo), Tymlos (abaloparatide subcutaneous injection), oral bisphosphonates (e.g., alendronate, risedronate, ibandronate), intravenous bisphosphonates (zoledronic acid intravenous infusion [Reclast], ibandronate intravenous infusion), calcitonin nasal spray (Miacalcin/Fortical), and Evenity (romosozumab-aqqg subcutaneous injection). Prolia is not indicated for use as combination therapy.[1] However, this does NOT exclude use of calcium and/or vitamin D supplements in combination with Prolia.

37. Giant Cell Tumor of Bone. Studies with denosumab in giant cell tumor of the bone used dosing for Xgeva, which is indicated for the treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.[2]

38. Osteoporosis Prevention. Prolia is not indicated for the prevention of osteoporosis.[1]

39. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Bone Modifiers – Teriparatide Products Prior Authorization Policy
- Forteo® (teriparatide subcutaneous injection – Eli Lilly, generic)
- Teriparatide subcutaneous injection – Alvogen

REVIEW DATE: 09/27/2023

OVERVIEW

d) Teriparatide products, which are parathyroid hormone analogs (PTH 1-34), are indicated for the following uses:[1,2,13,14]

- **Glucocorticoid-induced osteoporosis (treatment)**, in men and women at high risk for fracture associated with sustained systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone).
- **Osteoporosis, treatment of postmenopausal women** at high risk for fracture.
- **Osteoporosis, to increase bone mass in men with primary or hypogonadal osteoporosis** at high risk for fracture.

e)

f) In general, for all indications, patients at high risk for fracture are defined as those with a history of osteoporotic fractures, have multiple risk factors for fracture, or have failed or are intolerant to other osteoporosis therapy.[1,2]

Teriparatide has been used for patients with hypoparathyroidism.[3-6] Natpara® (parathyroid hormone subcutaneous injection) is indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism.[7] However, there is a recall of Natpara and teriparatide is one of two main alternatives recommended in a joint guidance statement from the American Society for Bone and Mineral Research and Endocrine Society for patients with hypoparathyroidism transitioning from Natpara.[8] It is notable that if teriparatide therapy is used in this clinical scenario, twice daily or even three times daily injections are usually needed.

Guidelines

Teriparatide is addressed in various clinical guidelines.[9-11]

- **Glucocorticoid-Induced Osteoporosis:** The American College of Rheumatology updated guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis (2017).[9] In various clinical scenarios, teriparatide is recommended after trial of other agents (e.g., oral bisphosphonates, intravenous bisphosphonates).
- **Postmenopausal Osteoporosis:** Teriparatide products are mentioned in guidelines for postmenopausal osteoporosis by the Endocrine Society (2019)[10] and the American Association of Clinical Endocrinologists and the American College of Endocrinology (2020)[11]. Teriparatide is one of several agents cited as an alternative for patients at very high risk for fractures or among those who cannot tolerate oral therapy. The Bone Health and Osteoporosis Foundation clinician guide for the prevention and treatment of osteoporosis (2022) cite robust reductions in vertebral and non-vertebral fractures with teriparatide.[12]

Safety

An increased incidence of osteosarcoma was noted in male and female rats who received teriparatide.[1] Osteosarcoma has been reported in patients treated with teriparatide in the post-marketing setting, however, an increased risk of osteosarcoma has not been observed in observational studies involving humans. There are limited data evaluating the risk of osteosarcoma beyond 2 years of teriparatide use. Avoid use of teriparatide in patients with a baseline risk of osteosarcoma. Use of teriparatide for more than 2 years during a patient's lifetime should only be considered if a patient remains at or has returned to having a high risk for fracture.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of teriparatide products. All approvals are provided for the duration noted below. For the indication of hypoparathyroidism, because of the specialized skills required for evaluation and diagnosis of patients treated with teriparatide as well as monitoring for adverse events and long-term efficacy, approval requires teriparatide to be prescribed by or in consultation with a physician who specializes in the condition being treated. In the approval indication, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Automation: Smart Coverage Review uses patient claim history to answer Prior Authorization questions regarding medication history of Boniva® (ibandronate intravenous injection) or Reclast® (zoledronic acid intravenous infusion). A 2-year look back period will be used to check claim history and automate for use of either agent (Boniva intravenous or Reclast). If not in claims, medication can be obtained through Prior Authorization criteria. For all reviews, other Prior Authorization criteria listed below will also be applied.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of teriparatide products is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Glucocorticoid-Induced Osteoporosis – Treatment.** Approve for the duration noted below if the patient meets the following (A, B, and C):
   - **C)** Patient is either initiating or continuing systemic glucocorticoids; AND
     Note: An example of a systemic glucocorticoid is prednisone.
   - **D)** Patient meets ONE of the following (i, ii, iii, or iv):
     - **v.** Patient has tried zoledronic acid intravenous infusion (Reclast); OR
     - **vi.** Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a or b):
       Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).
       - **c)** According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR
         Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.
       - **d)** Patient has experienced significant intolerance to an oral bisphosphonate; OR

Note: Examples of significant intolerance include severe gastrointestinal-related adverse events and/or severe musculoskeletal related-adverse events.

vii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):

g) Patient cannot swallow or has difficulty swallowing; OR

h) Patient cannot remain in an upright position post oral bisphosphonate administration; OR

i) Patient has a preexisting gastrointestinal medical condition; OR

Note: Examples of preexisting gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

viii. Patient meets one of the following conditions (a, b, or c):

d) Severe renal impairment; OR

Note: An example of severe renal impairment is a creatinine clearance < 35 mL/min.

e) Chronic kidney disease; OR

f) Patient has had an osteoporotic fracture or a fragility fracture; AND

E) Approve for one of the following (i or ii):

i. According to the prescriber, if the patient is at high risk for fracture, approve for one of the following (a or b):

Note: Examples of high risk for fracture include a previous osteoporotic fracture or fragility fracture, receipt of medications that increase the risk of osteoporosis, advanced age, and very low bone mineral density.

a) If patient is initiating therapy or has received a teriparatide product for < 1 year, approve for up to 2 years; OR

Note: For example, a patient who has already received 3 months of treatment with teriparatide should be approved for a duration of 21 months. This allows for completion of 2 years of therapy. Use of a teriparatide product beyond 2 years is evaluated annually for continued high risk of fracture.

b) If patient has already received ≥ 1 year of therapy with a teriparatide product, approve for 1 year.

Note: Use of a teriparatide product beyond 2 years is evaluated annually for continued high risk of fracture.

ii. According to the prescriber, if the patient is not at high risk for fracture, approve for the duration necessary to complete a maximum of 2 years of therapy (total) during a patient's lifetime.

Note: For example, a patient who has already received 3 months of treatment with teriparatide should be approved for a duration of 21 months. This allows for completion of a maximum of 2 years of therapy.

2. Osteoporosis Treatment for a Postmenopausal Patient. Approve for the duration noted below if the patient meets the following (A, B, and C):

A) Patient meets ONE of the following conditions (i, ii, or iii):

i. Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist); OR

ii. Patient has had an osteoporotic fracture or a fragility fracture; OR

iii. Patient meets both of the following (a and b):

a) Patient has low bone mass; AND

B) Note: An example of low bone mass includes a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip and/or 33% (one-third) radius (wrist).

b) According to the prescriber, patient is at high risk for fracture; AND

C) Patient meets ONE of the following (i, ii, iii, or iv):

i. Patient has tried ibandronate intravenous injection (Boniva) or zoledronic acid intravenous infusion (Reclast); OR

ii. Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a or b):

Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).

a) According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR

Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.

b) Patient has experienced significant intolerance to an oral bisphosphonate; OR

Note: Examples of significant intolerance include severe gastrointestinal-related adverse events and/or severe musculoskeletal-related adverse events.

iii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):

a) Patient cannot swallow or has difficulty swallowing; OR

b) Patient cannot remain in an upright position post oral bisphosphonate administration; OR

c) Patient has a preexisting gastrointestinal medical condition; OR

Note: Examples of preexisting gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

iv. Patient meets one of the following conditions (a, b, or c):

a) Severe renal impairment; OR

Note: An example of severe renal impairment is a creatinine clearance < 35 mL/min.

b) Chronic kidney disease; OR

c) Patient has had an osteoporotic fracture or a fragility fracture; AND

D) Approve for one of the following (i or ii):

i. According to the prescriber if the patient is at high risk for fracture, approve for one of the following (a or b):

Note: Examples of high risk for fracture include a previous osteoporotic fracture or fragility fracture, receipt of medications that increase the risk of osteoporosis, advanced age, and very low bone mineral density.

a) If patient is initiating therapy or has received a teriparatide product for < 1 year, approve for up to 2 years; OR

Note: For example, a patient who has already received 3 months of treatment with teriparatide should be approved for a duration of 21 months. This allows for completion of 2 years of therapy. Use of a teriparatide product beyond 2 years is evaluated annually for continued high risk of fracture.

b) If patient has already received ≥ 1 year of therapy with a teriparatide product, approve for 1 year.

Note: Use of a teriparatide product beyond 2 years is evaluated annually for continued high risk of fracture.

ii. According to the prescriber if the patient is not at high risk for fracture, approve for the duration necessary to complete a maximum of 2 years of therapy (total) during a patient's lifetime.

Note: For example, a patient who has already received 3 months of treatment with teriparatide should be approved for a duration of 21 months. This allows for completion of a maximum of 2 years of therapy.

3. **Osteoporosis Treatment (to Increase Bone Mass) for Men* with Primary or Hypogonadal Osteoporosis.** Approve for the duration noted below if the patient meets the following (A, B, and C):
   A) Patient meets ONE of the following conditions (i, ii, or iii):
      i. Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip and/or 33% (one-third) radius (wrist); OR
      ii. Patient has had an osteoporotic fracture or a fragility fracture; OR
      iii. Patient meets both of the following (a and b):
         a) Patient has low bone mass; AND
            Note: An example of low bone mass includes a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip and/or 33% (one-third) radius (wrist).
         b) According to the prescriber, patient is at high risk for fracture; AND
   B) Patient meets one of the following (i, ii, iii, or iv):
      i. Patient has tried zoledronic acid intravenous infusion (Reclast); OR
      ii. Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a or b):
         Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).
         a) According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR
            Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.
         b) Patient has experienced significant intolerance to an oral bisphosphonate; OR
            Note: Examples of significant intolerance include severe gastrointestinal-related adverse events and/or severe musculoskeletal-related adverse events.
      iii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):
         a) Patient cannot swallow or has difficulty swallowing; OR
         b) Patient cannot remain in an upright position post oral bisphosphonate administration; OR
         c) Patient has a preexisting gastrointestinal medical condition; OR
            Note: Examples of preexisting gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying (e.g., stricture, achalasia).
      iv. Patient meets one of the following conditions (a, b, or c):
         a) Severe renal impairment; OR
            Note: An example of severe renal impairment is a creatinine clearance < 35 mL/min.
         b) Chronic kidney disease; OR
         c) Patient has had an osteoporotic fracture or a fragility fracture; AND
   C) Approve for one of the following (i or ii):
      i. According to the prescriber if the patient is at high risk for fracture, approve for one of the following (a or b):
         Note: Examples of high risk for fracture include a previous osteoporotic fracture or fragility fracture, receipt of medications that increase the risk of osteoporosis, advanced age, and very low bone mineral density.
         a) If patient is initiating therapy or has received a teriparatide product for < 1 year, approve for up to 2 years; OR
            Note: For example, a patient who has already received 3 months of treatment with teriparatide should be approved for a duration of 21 months. This allows for completion

of 2 years of therapy. Use of a teriparatide product beyond 2 years is evaluated annually for continued high risk of fracture.

b) If patient has already received ≥ 1 year of therapy with a teriparatide product, approve for 1 year.
Note: Use of a teriparatide product beyond 2 years is evaluated annually for continued high risk of fracture.

ii. According to the prescriber if the patient is not at high risk for fracture, approve for the duration necessary to complete a maximum of 2 years of therapy (total) during a patient's lifetime.
Note: For example, a patient who has already received 3 months of treatment with teriparatide should be approved for a duration of 21 months. This allows for completion of a maximum of 2 years of therapy.

***** Refer to the Policy Statement.

Other Uses with Supportive Evidence

4. Hypoparathyroidism. Approve for 1 year if the patient meets the following (A and B):
1. Patient meets one of the following (i or ii):
   i. Patient has tried Natpara (parathyroid hormone subcutaneous injection); OR
   ii. Natpara is not available; AND
   Note: Approval for this use is a unique circumstance and the other criterion regarding the other indications do not apply.
2. Medication is prescribed by or in consultation with an endocrinologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of teriparatide is not recommended in the following situations:

40. Concurrent Use with Other Medications for Osteoporosis.
Note: Examples of medications for osteoporosis that teriparatide should not be given with include Prolia (denosumab subcutaneous injection), oral bisphosphonates (e.g., alendronate, risedronate, ibandronate), intravenous bisphosphonates (zoledronic acid intravenous infusion [Reclast], intravenous ibandronate), calcitonin nasal spray (Miacalcin/Fortical), Tymlos (abaloparatide subcutaneous injection), and Evenity (romosozumab-aqqg subcutaneous injection). However, this does NOT exclude use of calcium and/or vitamin D supplements in combination with teriparatide.

41. Osteoporosis Prevention. Teriparatide products have not been studied in this patient population. The benefits and risks of building bone with teriparatide products in a condition in which substantial bone loss has not occurred have not been investigated.[1]

42. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Bone Modifiers – Tymlos Prior Authorization Policy
- Tymlos® (abaloparatide subcutaneous injection – Radius)

REVIEW DATE: 09/27/2023

OVERVIEW

Tymlos, a human parathyroid hormone related peptide analog, is indicated for the following uses:[1]
- **Osteoporosis, treatment of postmenopausal women**, at high risk for fracture.
- **Osteoporosis, treatment to increase bone density in men**, at high risk for fracture.

Patients at high risk for fracture are defined as those with a history of osteoporotic fracture, have multiple risk factors for fracture, or have failed or are intolerant to other osteoporosis therapy.

Guidelines

Guidelines for osteoporosis in postmenopausal women from the Endocrine Society (2019)[2] as well as from the American Association of Clinical Endocrinologists and the American College of Endocrinology (2020)[3] discuss Tymlos. In general, Tymlos is one of several alternatives recommended in patients who are at high risk of fracture or in those unable to utilize oral bisphosphonate therapy. The Bone Health and Osteoporosis clinician guide to prevent and treat osteoporosis (2022) cites robust reductions in vertebral and non-vertebral fractures with Tymlos therapy in postmenopausal women with osteoporosis.[4]

Safety

The prescribing information for Tymlos states that the safety and efficacy of Tymlos have not been evaluated beyond 2 years of therapy. Use of the medication for more than 2 year during a patient's lifetime is not recommended. There are limited data evaluating the risk of osteosarcoma beyond 2 years of Tymlos and/or use of a parathyroid hormone analog. Avoid use of Tymlos in patients who are at increased baseline risk of osteosarcoma (e.g., open epiphyses [pediatric and young adult patients], those with metabolic bone disease, patients with bone metastases or a history of skeletal malignancies).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tymlos. All approvals are provided for the duration noted below. In the approval indication, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Automation: Smart Coverage Review uses patient claim history to answer Prior Authorization questions regarding medication history of Boniva® (ibandronate intravenous injection) or Reclast® (zoledronic acid intravenous infusion). A 2-year look back period will be used to check claim history and automate for use of either agent (Boniva intravenous injection or Reclast). If not in claims, medication can be obtained through Prior Authorization criteria. For all reviews, other Prior Authorization criteria listed below will also be applied.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Tymlos is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Osteoporosis Treatment for a Postmenopausal Patient.** Approve for up to 2 years (total) during a patient's lifetime if the patient meets the following (A and B):
   Note: For example, a patient who has already received 3 months of treatment with Tymlos should be approved for a duration of 21 months. This allows for completion of a maximum of 2 years of therapy during the patient's lifetime.
   E) Patient meets ONE of the following conditions (i, ii, or iii):
      iv. Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip and/or 33% (one-third) radius (wrist); OR
      v. Patient has had an osteoporotic fracture or a fragility fracture; OR
      vi. The patient meets both of the following (a and b):
         a) Patient has low bone mass; AND
            Note: An example of low bone mass includes a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist).
         b) According to the prescriber, patient is at high risk for fracture; AND
   F) Patient meets ONE of the following (i, ii, iii, or iv):
      v. Patient has tried ibandronate intravenous injection (Boniva) or zoledronic acid intravenous infusion (Reclast); OR
      vi. Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a or b):
         Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).
         c) According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR
            Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack or a BMD increase, and/or an osteoporotic fracture or a fragility fracture.
         d) Patient has experienced significant intolerance to an oral bisphosphonate; OR
            Note: Examples of significant intolerance include severe gastrointestinal related adverse events and/or severe musculoskeletal related adverse events.
      vii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):
         a) Patient cannot swallow or has difficulty swallowing; OR
         b) Patient cannot remain in an upright position post oral bisphosphonate administration; OR
         c) Patient has a pre-existing gastrointestinal medical condition; OR
            Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).
      viii. Patient meets one of the following conditions (a, b, or c):
         d) Severe renal impairment; OR
            Note: An example of severe renal impairment is a creatinine clearance < 35 mL/min.
         e) Chronic kidney disease; OR
         f) Patient has had an osteoporotic fracture or a fragility fracture.

2. Osteoporosis Treatment for Men*. Approve for up to 2 years (total) during a patient's lifetime if the patient meets the following (A and B):
Note: For example, a patient who has already received 3 months of treatment with Tymlos should be approved for a duration of 21 months. This allows for completion of a maximum of 2 years of therapy during the patient's lifetime.

A) Patient meets ONE of the following conditions (i, ii, or iii):
- **i.** Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip and/or 33% (one-third) radius (wrist); OR
- **ii.** Patient has had an osteoporotic fracture or a fragility fracture; OR
- **iii.** The patient meets both of the following (a and b):
  - **a)** Patient has low bone mass; AND
    Note: An example of low bone mass includes a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist).
  - **b)** According to the prescriber, patient is at high risk for fracture; AND

B) Patient meets ONE of the following (i, ii, iii, or iv):
- **i.** Patient has tried zoledronic acid intravenous infusion (Reclast); OR
- **ii.** Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a or b):
  Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).
  - **a)** According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR
    Note: Examples of an inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack or a BMD increase, and/or an osteoporotic fracture or a fragility fracture.
  - **b)** Patient has experienced significant intolerance to an oral bisphosphonate; OR
    Note: Examples of significant intolerance include severe gastrointestinal related adverse events and/or severe musculoskeletal related adverse events.
- **iii.** Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):
  - **a)** Patient cannot swallow or has difficulty swallowing; OR
  - **b)** Patient cannot remain in an upright position post oral bisphosphonate administration; OR
  - **c)** Patient has a pre-existing gastrointestinal medical condition; OR
    Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).
- **iv.** Patient meets one of the following conditions (a, b, or c):
  - **a)** Severe renal impairment; OR
    Note: An example of severe renal impairment is a creatinine clearance < 35 mL/min.
  - **b)** Chronic kidney disease; OR
  - **c)** Patient has had an osteoporotic fracture or a fragility fracture.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tymlos is not recommended in the following situations:

43. Concurrent Use with Other Medications for Osteoporosis.

Note: Examples of medications for osteoporosis that Tymlos should not be given with include Prolia (denosumab subcutaneous injection), oral bisphosphonates (alendronate, risedronate, ibandronate), intravenous bisphosphonates (zoledronic acid intravenous infusion [Reclast], ibandronate intravenous injection), calcitonin nasal spray (Miacalcin/Fortical), teriparatide subcutaneous injection (Forteo), and Evenity (romosozumab-aqqg subcutaneous injection). However, this does NOT exclude use of calcium and/or vitamin D supplements in combination with Tymlos.

44. Osteoporosis Prevention. Tymlos has not been studied in this patient population. The benefits and risks of building bone with Tymlos in a condition in which substantial bone loss has not occurred have not been investigated.[1]

45. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Bone Modifiers – Xgeva Prior Authorization Policy
- Xgeva® (denosumab subcutaneous injection – Amgen)

REVIEW DATE: 03/22/2023

OVERVIEW

Xgeva, a receptor activator of nuclear factor kappa-B ligand inhibitor, is indicated for the following uses:[1]

- **Giant cell tumor of bone**, treatment of adults and skeletally mature adolescents with disease that is unresectable or where surgical resection is likely to result in severe morbidity.
- **Hypercalcemia of malignancy**, treatment of, that is refractory to bisphosphonate therapy.
- **Skeletal-related events**, prevention of, in patients with multiple myeloma and in those with bone metastases from solid tumors.

Another injectable formulation of denosumab is available, Prolia® (subcutaneous injection), but it is not included in this policy.[2]

Guidelines

Several guidelines address Xgeva.

- **Cancer:** Various guidelines from the National Comprehensive Cancer Network (e.g., breast cancer, prostate cancer, lung cancer, multiple myeloma) recommend Xgeva for the prevention of skeletal related adverse events.[3-6]
- **Hypercalcemia of Malignancy:** Guidelines from the Endocrine Society for the treatment of hypercalcemia of malignancy in adults (2023) have several recommendations.[7] In adults with hypercalcemia of malignancy, treatment with Xgeva over an intravenous bisphosphonate is recommended.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Xgeva. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Xgeva as well as the monitoring required for adverse events and long-term efficacy, approval requires Xgeva to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xgeva is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Bone Metastases from Solid Tumors – Prevention of Skeletal-Related Events.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
   Note: Some examples of cancer in this clinical scenario include breast cancer, prostate cancer, and non-small cell lung cancer.

A) Patient is ≥ 18 years of age; AND
B) Patient has bone metastases; AND
C) Patient with prostate cancer must have castration-resistant prostate cancer; AND
Note: This includes patients who have progressed after treatment with hormonal therapy or after surgical castration (e.g., bilateral orchiectomy). Examples of hormonal therapies for prostate cancer include Lupron Depot (leuprolide for depot suspension), Eligard (leuprolide acetate for injectable suspension), Trelstar (triptorelin pamoate for injectable suspension), or Zoladex (goserelin implant).
D) The medication is prescribed by or in consultation with a hematologist or an oncologist.

2. **Giant Cell Tumor of Bone.** Approve for 1 year.

3. **Hypercalcemia of Malignancy.** Approve for 2 months if the patient meets the following criteria (A and B):
A) Patient has a current malignancy; AND
B) Patient has an albumin-corrected calcium (cCa) ≥ 11.5 mg/dL.

4. **Multiple Myeloma – Prevention of Skeletal-Related Events.** Approve for 1 year if the patient meets the following criteria (A and B):
A) Patient is ≥ 18 years of age; AND
B) Medication is prescribed by or in consultation with a hematologist or an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xgeva is not recommended in the following situations:

26. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Bone Modifiers – Zoledronic Acid (Reclast) Prior Authorization Policy
- Reclast® (zoledronic acid intravenous infusion – Novartis, generic)

REVIEW DATE: 03/22/2023

OVERVIEW

Zoledronic acid (Reclast), a bisphosphonate given intravenously, is indicated for the following uses:[1]

- **Glucocorticoid-induced osteoporosis**, for treatment and prevention in men and women who are either initiating or continuing systemic glucocorticoids (e.g., prednisone 7.5 mg or greater) and who are anticipated to remain on glucocorticoids for at least 12 months.
- **Osteoporosis, prevention in postmenopausal women**.
- **Osteoporosis, treatment in men** to increase bone mass.
- **Osteoporosis, treatment in postmenopausal women**.
- **Paget's disease of bone**, treatment in men and women.

Another zoledronic acid injection product, Zometa®, is indicated for hypercalcemia of malignancy; and for multiple myeloma and bone metastases from solid tumors.[2] Although not indicated, zoledronic acid injection (Reclast) has been used in patients, mainly children, with osteogenesis imperfecta and benefits were noted, such as increases in bone mineral density.[1,3-8]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of zoledronic acid injection (Reclast). All approvals are provided for the duration noted below. Regarding the approval duration of one dose, the approval is for 30 days, which is an adequate duration for the patient to receive one dose. In the approval indication for zoledronic acid injection (Reclast), as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of zoledronic acid injection (Reclast) is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Glucocorticoid-Induced Osteoporosis – Prevention and Treatment.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient is either initiating or continuing systemic glucocorticoids; AND
     Note: An example of a systemic glucocorticoid is prednisone.
   - **B)** Patient meets ONE of the following (i, ii, iii, or iv):
     - **i.** Patient has tried zoledronic acid intravenous infusion (Reclast); OR
     - **ii.** Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a or b):

Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).

a) According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR
Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.

b) Patient has experienced significant intolerance to an oral bisphosphonate; OR
Note: Examples of significant intolerance include severe gastrointestinal related adverse events, severe musculoskeletal related adverse events, and femoral fracture.

iii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):

a) Patient cannot swallow or has difficulty swallowing; OR

b) Patient cannot remain in an upright position post-oral bisphosphonate administration; OR

c) Patient has a pre-existing gastrointestinal medical condition in which intravenous bisphosphonate therapy may be warranted; OR
Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, and abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

iv. Patient has had an osteoporotic fracture or a fragility fracture.

2. Osteoporosis – Prevention for a Postmenopausal Patient. Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) Patient meets ONE of the following conditions (i or ii):

i. Patient has had a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one third) radius (wrist); OR

ii. Patient has had an osteoporotic fracture or a fragility fracture; AND

B) Patient meets ONE of the following (i, ii, iii, or iv):

i. Patient has tried zoledronic acid intravenous infusion (Reclast); OR

ii. Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a or b):
Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).

a) According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR
Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.

b) Patient has experienced significant intolerance to an oral bisphosphonate; OR
Note: Examples of significant intolerance include severe gastrointestinal related adverse events, severe musculoskeletal related adverse events, and femoral fracture.

iii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):

a) Patient cannot swallow or has difficulty swallowing; OR

b) Patient cannot remain in an upright position post oral bisphosphonate administration; OR

c) Patient has a pre-existing gastrointestinal medical condition in which intravenous bisphosphonate therapy may be warranted; OR

Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, and abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

iv. Patient has had an osteoporotic fracture or a fragility fracture; AND

C) If the patient has received Reclast previously, at least 24 months has elapsed since the last dose.

3. Osteoporosis – Treatment for a Man*. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient meets ONE of the following conditions (i, ii, or iii):

i. Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one third) radius (wrist); OR

ii. Patient has had an osteoporotic fracture or a fragility fracture; OR

iii. Patient meets both of the following (a and b):

a) Patient has low bone mass; AND

Note: An example of low bone mass includes a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip and/or 33% (one-third) radius (wrist).

b) According to the prescriber, patient is at high risk for fracture; AND

B) Patient meets ONE of the following (i, ii, iii, or iv):

i. Patient has tried zoledronic acid intravenous infusion (Reclast); OR

ii. Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a or b):

Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).

a) According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR

Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.

b) Patient has experienced significant intolerance to an oral bisphosphonate; OR

Note: Examples of significant intolerance include severe gastrointestinal related adverse events, severe musculoskeletal related adverse events, and femoral fracture.

iii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):

a) Patient cannot swallow or has difficulty swallowing; OR

b) Patient cannot remain in an upright position post oral bisphosphonate administration; OR

c) Patient has a pre-existing gastrointestinal medical condition in which intravenous bisphosphonate therapy may be warranted; OR

Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, and abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

iv. Patient has had an osteoporotic fracture or a fragility fracture.

***** Refer to the Policy Statement.

4. Osteoporosis – Treatment for a Postmenopausal Patient. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient meets ONE of the following conditions (i, ii, or iii):

i. Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist); OR

ii. Patient has had an osteoporotic fracture or a fragility fracture; OR

iii. Patient meets both of the following (a and b):

a) Patient has low bone mass; AND

Note: An example of low bone mass includes a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip and/or 33% (one-third) radius (wrist).

b) According to the prescriber, patient is at high risk for fracture; AND

B) Patient meets ONE of the following (i, ii, iii, or iv):

i. Patient has tried ibandronate intravenous infusion (Boniva IV) or zoledronic acid intravenous infusion (Reclast); OR

ii. Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a or b):

Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).

a) According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR

Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.

b) Patient has experienced significant intolerance to an oral bisphosphonate; OR

Note: Examples of significant intolerance include severe gastrointestinal related adverse events, severe musculoskeletal related adverse events, and femoral fracture.

iii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):

a) Patient cannot swallow or has difficulty swallowing; OR

b) Patient cannot remain in an upright position post oral bisphosphonate administration; OR

c) Patient has a pre-existing gastrointestinal medical condition in which intravenous bisphosphonate therapy may be warranted; OR

Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, and abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

iv. Patient has had an osteoporotic fracture or a fragility fracture.

5. Paget's Disease of Bone. Approve for one dose if the patient meets one of the following criteria (A, B, or C):

A) Patient has elevations in serum alkaline phosphatase of two times higher than the upper limit of the age-specific normal reference range; OR

B) Patient is symptomatic; OR

Note: Examples of symptoms include bone pain, hearing loss, and osteoarthritis.

C) Patient is at risk for complications from their disease.

Note: Examples of disease complications include immobilization, bone deformity, fractures and nerve compression syndrome.

Other Uses with Supportive Evidence

6. Osteogenesis Imperfecta. Approve for 1 year.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of zoledronic acid injection (Reclast) is not recommended in the following situations:

1. **Concurrent Use of Zoledronic Acid Intravenous Infusion (Reclast) with Other Medications for Osteoporosis.**
   Note: Examples of medications for osteoporosis that zoledronic acid intravenous infusion (Reclast) should not be given with include oral bisphosphonates (e.g., alendronate, risedronate, ibandronate), other intravenous bisphosphonates (e.g., intravenous ibandronate [Boniva]), Prolia (denosumab subcutaneous injection), Evenity (romosozumab-aqqg subcutaneous injection), Forteo (teriparatide subcutaneous injection, generic), Tymlos (abaloparatide subcutaneous injection), and calcitonin nasal spray. This only applies to the osteoporosis-related indications. However, this does NOT exclude use of calcium and/or vitamin D supplements in combination with zoledronic acid intravenous infusion (Reclast). This criterion applies only to osteoporosis-related indications.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Bone Modifiers – Zoledronic Acid (Zometa) Prior Authorization Policy
- Zometa® (zoledronic acid intravenous infusion – generic only)

REVIEW DATE: 03/22/2023

OVERVIEW

Zoledronic acid intravenous infusion (Zometa), a bisphosphonate, is indicated for the treatment of the following:[1]

- **Hypercalcemia of malignancy**.
- **Multiple myeloma and documented bone metastases from solid tumors**, in addition to standard antineoplastic therapy.

Prostate cancer should have progressed after treatment with at least one hormonal therapy.[1] Another formulation of zoledronic acid intravenous infusion (Reclast®) is available but is not included in this policy.[2]

Data are available with zoledronic acid intravenous infusion (Zometa) regarding off-label uses. One example is to prevent bone loss in patients with breast cancer receiving aromatase inhibitor therapy. Aromatase inhibitor therapy prevents peripheral production and suppresses estrogen levels and can lead to accelerated bone loss beyond what would naturally occur in women.[3,4] This can place the patient at an increased risk for having a fracture. A review on the management of aromatase inhibitor-associated bone loss in postmenopausal women with breast cancer[5] states that zoledronic acid intravenous infusion (Zometa) [4 mg every 6 months] is the preferred agent for prevention and treatment of aromatase inhibitor bone loss.[4] Zoledronic acid intravenous infusion (Zometa) has been studied and shown benefits in postmenopausal women receiving adjuvant letrozole for breast cancer.[5,6]

Zoledronic acid intravenous infusion (Zometa) has also been utilized to prevent bone loss in patients with prostate cancer who are receiving androgen deprivation therapy (ADT). ADT is associated with a variety of adverse events, including osteoporosis. The National Comprehensive Cancer Network (NCCN) clinical practice guidelines regarding prostate cancer (version 1.2023 – September 16, 2022)[7] cite zoledronic acid as an option to increase bone density, a surrogate for fracture risk, during ADT for prostate cancer. Zoledronic acid intravenous infusion (Zometa) has led to bone mineral density increases in patients with prostate cancer who are receiving androgen deprivation therapy.[8,9] A clinical practice guideline for osteoporosis in men from the Endocrine Society[9] recommends pharmacological treatment for osteoporosis for men with prostate cancer receiving ADT who have a high risk of fracture. Zoldedronic acid intravenous infusion (Zometa) has utility in premenopausal patients with breast cancer who have developed ovarian failure. Chemotherapy-induced ovarian failure is an adverse effect associated with some adjuvant chemotherapy and can lead to rapid bone loss.[10,11] Studies have demonstrated zoledronic acid intravenous infusion (Zometa) to be efficacious in preserving bone mineral density in premenopausal women with breast cancer who developed ovarian failure due to adjuvant chemotherapy.

The American Society of Clinical Oncology and the Cancer Care Ontario group updated guidelines for use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer. The guideline recommend adjuvant bisphosphonate therapy in postmenopausal patients with primary breast cancer who are candidates to receive adjuvant systemic therapy.[12] NCCN guidelines for breast cancer also recommend bisphosphonates as adjuvant therapy for postmenopausal women with breast cancer.[13]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of zoledronic acid intravenous infusion (Zometa). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with zoledronic acid intravenous infusion (Zometa) as well as the monitoring required for adverse events and long-term efficacy, approval requires zoledronic acid intravenous infusion (Zometa) to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of zoledronic acid intravenous infusion (Zometa) is recommended in those who meet one of the following criteria:

FDA-Approved Indications

25. **Bone Metastases From Solid Tumors – Prevention of Skeletal-Related Events.** Approve for 1 year if the patient meets all of the following criteria (A, B, and C):
    Note: Some examples of cancer in this clinical scenario include breast cancer, prostate cancer, non-small cell lung cancer, renal cell cancer, small cell lung cancer, colorectal cancer, bladder cancer, gastrointestinal/genitourinary cancer, and head and neck cancer.
    A) Patient has bone metastases; AND
    B) Patient with prostate cancer must have castration-resistant prostate cancer; AND
    Note: This includes patients who have progressed after treatment with hormonal therapy or after surgical castration (e.g., bilateral orchiectomy). Examples of hormonal therapies for prostate cancer include Lupron Depot (leuprolide for depot suspension), Eligard (leuprolide acetate for injectable suspension), Trelstar (triptorelin pamoate for injectable suspension), and Zoladex (goserelin implant).
    C) The medication is prescribed by or in consultation with a hematologist or an oncologist.

26. **Hypercalcemia of Malignancy.** Approve for 1 month if the patient meets the following criteria (A and B):
    A) Patient has a current malignancy; AND
    B) Patient has an albumin-corrected calcium (cCa) ≥ 11.5 mg/dL.

27. **Multiple Myeloma – Prevention of Skeletal-Related Events.** Approve for 1 year if the agent is prescribed by or in consultation with a hematologist or an oncologist.

Other Uses with Supportive Evidence

28. **Breast Cancer – Adjuvant Therapy.** Approve for 1 year if the patient is postmenopausal.

29. **Prevention of Bone Loss (To Increase Bone Mass) in a Patient with Breast Cancer Receiving Aromatase Inhibitor Therapy**. Approve for 1 year if the patient meets the following criteria (A and B):
    A) Patient has breast cancer that is not metastatic to bone; AND
    B) Patient is receiving an aromatase inhibitor therapy.

Note: Examples of aromatase inhibitor agents include anastrozole, letrozole, and exemestane.

30. **Prevention of Bone Loss (To Increase Bone Mass) in a Patient with Prostate Cancer Who are Receiving Androgen Deprivation Therapy (ADT).** Approve for 1 year if the patient meets the following criteria (A and B):
    - **A)** Patient has prostate cancer that is not metastatic to bone; AND
    - **B)** Patient meets one of the following (i or ii):
        - **i.** Patient is currently receiving androgen deprivation therapy; OR
          Note: Examples of androgen deprivation therapies include Lupron Depot (leuprolide for depot suspension), Eligard (leuprolide acetate for injectable suspension), Trelstar (triptorelin pamoate for injectable suspension), or Zoladex (goserelin implant).
        - **ii.** Patient has undergone bilateral orchiectomy.

31. **Prevention of Bone Loss (to Increase Bone Mass) in a Premenopausal Patient with Breast Cancer Who Has Developed Ovarian Failure.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
    - **A)** Patient is premenopausal; AND
    - **B)** Breast cancer is not metastatic to bone; AND
    - **C)** Patient received adjuvant chemotherapy that led to ovarian failure.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of zoledronic acid intravenous infusion (Zometa) is not recommended in the following situations:

27. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Botulinum Toxins – Botox Prior Authorization Policy
- Botox® (onabotulinumtoxinA injection – Allergan/AbbVie)

REVIEW DATE: 10/11/2023

OVERVIEW

Botox (onabotulinumtoxinA) is indicated for the following uses:[1]

- **Blepharospasm** associated with dystonia, including benign essential blepharospasm or seventh (VII) nerve disorders in patients ≥ 12 years of age.
- **Cervical dystonia,** in adults to reduce the severity of abnormal head position and neck pain associated with cervical dystonia.
- **Hyperhidrosis, severe primary axillary** which is inadequately managed with topical agents in adults.
- **Migraine headache prophylaxis (prevention),** in adults with chronic migraine (≥ 15 days per month with headache lasting 4 hours a day or longer).
- **Neurogenic detrusor overactivity** in pediatric patients ≥ 5 years of age who have had an inadequate response to or are intolerant of an anticholinergic medication.
- **Overactive bladder** with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have had an inadequate response to or are intolerant of an anticholinergic medication.
- **Spasticity** in patients ≥ 2 years of age.
- **Strabismus** in patients ≥ 12 years of age.
- **Urinary incontinence due to detrusor overactivity** associated with a neurological condition (e.g., spinal cord injury, multiple sclerosis) in adults who have had an inadequate response to or are intolerant of an anticholinergic medication.

In regard to the indication of migraine headache prophylaxis, an updated assessment of the preventive and acute treatment of migraine by the American Headache Society (2018; update 2021) notes that several medications are cited as having established or probable efficacy in migraine prevention.[4,35,36] Based on the level of evidence for efficacy and the American Academy of Neurology scheme for classification of evidence, the following oral treatments have established efficacy and should be offered for migraine prevention: antiepileptic drugs (divalproex sodium, valproate sodium, topiramate [not for women of childbearing potential without a reliable method of birth control]); beta-blockers (metoprolol, propranolol, timolol); and frovatriptan (for short-term preventive treatment of menstrual migraine). The following treatments are probably effective and should be considered for migraine prevention: antidepressants (amitriptyline, venlafaxine); beta-blockers (atenolol, nadolol); and angiotensin receptor blockers (candesartan). Additionally, the following treatments are possibly effective and can be considered for migraine prevention: calcium channel blockers (e.g., verapamil) and angiotensin converting enzyme inhibitors (e.g., lisinopril).[37,38]

Other Uses with Supportive Evidence

Botulinum toxin type A has been used to treat a multitude of disorders characterized by abnormal muscle contraction.[2] The benefit of these products has also been demonstrated in the treatment of gastrointestinal, genitourinary, ocular, and autonomic nervous system disorders.[2,3]

Botulinum toxins have been studied in a variety of indications outside of FDA-approved uses. Literature is available to support use of Botox in the following conditions:

- **Achalasia:** The American College of Gastroenterology (ACG) clinical guideline for the diagnosis and management of achalasia (2020) recommends the use of botulinum toxin as first-line therapy for patients with achalasia who are unfit for definitive therapies for the treatment of achalasia such as pneumatic dilation or surgical myotomy.[5]
- **Anal Fissures:** The ACG clinical guideline for the management of benign anorectal disorders (2021) suggests that botulinum toxin A injections may be attempted for patients in whom calcium channel blockers fail or as an alternative option to calcium channel blockers (conditional recommendation; quality of evidence low).[6]
- **Chronic Facial Pain/Pain Associated with Temporomandibular Dysfunction:** Data from several open-label studies, as well as one randomized, placebo-controlled trial, support the efficacy of Botox in the treatment of chronic facial pain/chronic facial pain associated with hyperactivity of the masticatory muscles.[7-10]
- **Chronic Low Back Pain:** In one 8-week, randomized, double-blind, placebo-controlled trial in 31 patients with chronic low back pain (no causative factor identified in the majority of patients; of disc disease in 6 patients, discectomy in 3 patients, and trauma in 4 patients), Botox in addition to their current pharmacologic treatment regimen resulted in significantly greater improvement in pain relief and degree of disability compared with placebo.[11] A 14-month, open-label, prospective study evaluated the short- and long-term effects of paraspinal muscle injections of Botox in 75 patients with refractory chronic low back pain. A total of 53% and 52% of patients reported significant pain relief at 3 weeks and 2 months, respectively.[12]
- **Dystonia, other than Cervical:** Guidelines from the American Academy of Neurology (AAN) support use of botulinum toxins in focal dystonias of the upper extremity (should be considered; Level B recommendation).[13] Botulinum toxin A is the most widely accepted treatment for spasmodic dysphonia, a focal laryngeal dystonia, viewed as the treatment of choice by the American Academy of Otolaryngology-Head and Neck Surgery.[14] Per the guideline, clinicians should offer, or refer to a clinician who can offer, botulinum toxin injections for treatment of dysphonia caused by spasmodic dysphonia and other types of laryngeal dystonia. AAN guidelines note that botulinum toxin is probably effective and should be considered for adductor type laryngeal dystonia (Level B).[13]
- **Essential Tremor:** According to the clinical practice parameter on essential tremor by the AAN, propranolol and primidone are first-line therapy in the treatment of essential tremor.[15] Second-line medication options include alprazolam, atenolol, sotalol, gabapentin, and topiramate. Botulinum toxin A may also reduce tremor. The guidelines recommend that botulinum toxin A may be considered in medically refractory cases of limb, head, and voice tremor associated with essential tremor (Level C for limb, head, and voice tremor).
- **Hemifacial Spasm:** Per the AAN, botulinum toxin (formulation not specified) may be considered in hemifacial spasm (Level C).[13] Data with Botox and Dysport® (abobotulinumtoxinA injection) are cited in the recommendations regarding hemifacial spasm.
- **Hyperhidrosis, Gustatory:** Botox is recommended as a first-line option for gustatory sweating by the International Hyperhidrosis Society.[16]
- **Hyperhidrosis, Palmar/Plantar and Facial:** The efficacy of Botox is well-established in the treatment of primary focal/palmar hyperhidrosis based on data from both randomized, double-blind, placebo-controlled studies and open-label studies.[3,18,19] Guidelines from the International Hyperhidrosis Society support use of Botox in patients who have failed to respond to topical therapy.[16,20,21]
- **Myofascial Pain:** Data from several retrospective reviews and open-label trials support the efficacy of Botox in the treatment of myofascial pain syndromes associated with various muscle groups.[7,22] In one randomized, controlled trial in 40 patients with chronic myofascial pain of various forms, Botox resulted in a significantly greater reduction in pain score from baseline

compared with intramuscularly administered methylprednisolone at 30 days and 60 days post injection.[23,24]

- **Ophthalmic Disorders, other than Blepharospasm or Strabismus:** Botulinum toxin A has been successful in improving or treating many ophthalmic disorders. One retrospective review (n = 54) concluded that Botox may have a role in the treatment of esotropia in patients > 18 months of age.[25] Botox improved visual acuity in case reports and one small, open-label study in patients with acquired symptomatic nystagmus from multiple sclerosis or brain-stem hemorrhage.[26,27] Data from uncontrolled studies have shown Botox to be beneficial in the treatment of sixth nerve palsy.[28,29]
- **Plantar Fasciitis:** In one randomized, double-blind study (n = 36), botulinum toxin A exhibited more rapid and sustained improvement over the duration of the study as compared with patients who received steroid injections.[30] The clinical consensus statement on the diagnosis and treatment of heel pain (developed by the American College of Foot and Ankle Surgeons) published in 2010 list botulinum toxin injection as a Tier 2 option (Grade I); Tier 1 treatment options include: padding and strapping of the foot (Grade B), therapeutic orthotic insoles (Grade B), oral anti-inflammatory agents (Grade I), corticosteroid injections (Grade B), and Achilles and plantar fascia stretching (Grade B) [Grade B recommendations are supported by fair evidence, Grade I recommendations indicate there is insufficient evidence to make a recommendation].[31]
- **Sialorrhea, Chronic:** Botulinum toxin A has been studied in the treatment of sialorrhea associated with Parkinson's Disease, parkinsonian syndromes, cerebral palsy, head and neck carcinoma, neurodegenerative disease, stroke, and amyotrophic lateral sclerosis.[3] A review of the literature on medical treatment of sialorrhea found that Botox is probably effective for the treatment of this condition (level B evidence).[32]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Botox. All approvals are provided for the duration noted below. Previous therapy is required to be verified by a clinician in the Coverage Review Department when noted in the criteria as **[verification of therapies required]**.

Prescription benefit coverage is not recommended for Botox Cosmetic or cosmetic conditions.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Botox is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Blepharospasm.** Approve for 1 year if the patient is ≥ 12 years of age.
   Note: This includes blepharospasm associated with dystonia, benign essential blepharospasm, seventh (VII) nerve disorders.

2. **Cervical Dystonia.** Approve for 1 year if the patient is ≥ 18 years of age.
   Note: Cervical dystonia is also referred to as spasmodic or cervical torticollis.

3. **Hyperhidrosis, Primary Axillary**. Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has tried at least one topical agent for axillary hyperhidrosis.
   Note: Examples of topical agents for the treatment of axillary hyperhidrosis include topical aluminum chloride, Qbrexza (glycopyrronium cloth 2.4% for topical use).

4. **Migraine Headache Prevention.** Approve for 1 year if the patient meets the following (A, B, C, D, E and F):

A) Patient is ≥ 18 years of age; AND

B) Patient has ≥ 15 migraine headache days per month with headache lasting 4 hours per day or longer (prior to initiation of Botox therapy); AND

C) Patient has tried at least TWO standard prophylactic (preventative) pharmacologic therapies, each from a different pharmacologic class **[verification of therapies required]**; AND

Note: Standard prophylactic (preventative) pharmacologic therapies include angiotensin receptor blocker, angiotensin converting enzyme inhibitor, anticonvulsant, beta-blocker, calcium channel blocker, tricyclic antidepressant, other antidepressant. A patient who has already tried a calcitonin gene-related peptide (CGRP) inhibitor indicated for the prevention of chronic migraine, is NOT required to try two standard prophylactic pharmacologic therapies **[verification of therapy required]**.

D) Patient meets ONE of the following (i, ii, or iii):

- **i.** Patient has had inadequate efficacy to both of those standard prophylactic (preventive) pharmacologic therapies, according to the prescriber; OR
- **ii.** Patient has experienced adverse event(s) severe enough to warrant discontinuation of both of those standard prophylactic (preventive) pharmacologic therapies, according to the prescriber; OR
- **iii.** Patient has had inadequate efficacy to one standard prophylactic (preventive) pharmacologic therapy and has experienced adverse event(s) severe enough to warrant discontinuation to another standard prophylactic (preventive) pharmacologic therapy, according to the prescriber; AND

E) Botox is being prescribed by or after consultation with a neurologist or headache specialist; AND

F) If the patient is currently taking Botox for migraine headache prevention, the patient has had a significant clinical benefit from the medication as determined by the prescriber.

Note: Examples of significant clinical benefit include a reduction in the overall number of migraine days per month or a reduction in number of severe migraine days per month from the time that Botox was initiated.

5. **Neurogenic Detrusor Overactivity (NDO), Pediatric**. Approve for 1 year if the patient meets the following (A and B):

A) Patient is ≥ 5 years of age; AND

B) Patient has tried at least one other pharmacologic therapy for the treatment of neurogenic detrusor overactivity (NDO).

Note: Examples of other NDO pharmacologic therapies include a beta-3 adrenergic agonist or an anticholinergic medication.

6. **Overactive Bladder with Symptoms of Urge Urinary Incontinence, Urgency, and Frequency (Adult)**. Approve for 1 year if the patient meets the following (A and B):

A) Patient is ≥ 18 years of age; AND

B) Patient has tried at least one other pharmacologic therapy for the treatment of overactive bladder (OAB).

Note: Examples of other OAB pharmacologic therapies include a beta-3 adrenergic agonist or an anticholinergic medication. For treatment of adult urinary incontinence associated with a neurological condition, refer to FDA-Approved Indications below.

7. **Spasticity, Limb**. Approve for 1 year if the is patient ≥ 2 years of age.

8. **Strabismus.** Approve for 1 year if the patient is ≥ 12 years of age.

9. **Urinary Incontinence Associated with a Neurological Condition (Adult)**. Approve for 1 year if the patient meets the following (A and B):
   Note: Examples of neurological conditions associated with urinary incontinence include spinal cord injury, multiple sclerosis, spina bifida.
   A) Patient is ≥ 18 years of age; AND
   B) Patient has tried at least one other pharmacologic therapy for the treatment of urinary incontinence.
   Note: Examples of other pharmacologic therapies for urinary incontinence include a beta-3 adrenergic agonist or an anticholinergic medication. For treatment of adult overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, see FDA-Approved Indications above.

Other Uses with Supportive Evidence

10. **Achalasia**. Approve for 1 year if the patient is ≥ 18 years of age.

11. **Anal Fissure.** Approve for 1 year if the patient is ≥ 18 years of age.

12. **Chronic Facial Pain/Pain Associated with Temporomandibular Dysfunction.** Approve for 1 year if the patient is ≥ 18 years of age.

13. **Chronic Low Back Pain.** Approve for 1 year if the patient meets the following (A, B and C):
A) Patient is ≥ 18 years of age; AND
B) Patient has tried at least TWO other pharmacologic therapies for treatment of chronic low back pain; AND
   Note: Examples of pharmacologic therapies include nonsteroidal anti-inflammatory drugs (NSAIDs), antispasmodics, muscle relaxants, opioids, or antidepressants.
C) Botox is being used as part of a multimodal therapeutic pain management program.

14. **Dystonia, other than Cervical.** Approve for 1 year if the patient is ≥ 18 years of age.
   Note: Examples of dystonias include focal dystonias, tardive dystonia, anismus, or laryngeal dystonia/spasmodic dysphonia. For cervical dystonia, refer to FDA-Approved Indications above.

15. **Essential Tremor.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has tried at least one other pharmacologic therapy for the treatment of tremors.
   Note: Examples of pharmacologic therapies for essential tremor include primidone, propranolol, benzodiazepines, gabapentin, or topiramate.

16. **Hemifacial Spasm.** Approve for 1 year if the patient is ≥ 18 years of age.

17. **Hyperhidrosis, Gustatory.** Approve for 1 year if the patient is ≥ 18 years of age.
   Note: Gustatory hyperhidrosis is also referred to as Frey's Syndrome.

18. **Hyperhidrosis, Palmar/Plantar and Facial.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND

B) Patient has tried at least one topical agent for the treatment of hyperhidrosis (e.g., aluminum chloride).

19. Myofascial Pain. Approve for 1 year if the patient is ≥ 18 years of age.

20. Ophthalmic Disorders, other than Blepharospasm or Strabismus. Approve for 1 year if the patient is ≥ 18 years of age.
Note: Examples of ophthalmic disorders include esotropia, exotropia, nystagmus, or facial nerve paresis. For blepharospasm or strabismus, refer to FDA-Approved Indications above.

21. Plantar Fasciitis. Approve for 1 year if the patient meets the following (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient has tried TWO other treatment modalities for the treatment of plantar fasciitis.
Note: Examples of other treatment modalities include padding and strapping of the foot, therapeutic orthotic insoles, oral anti-inflammatory drugs, corticosteroid injections, stretching.

22. Sialorrhea, Chronic. Approve for 1 year if the patient is ≥ 18 years of age.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Botox is not recommended in the following situations:

1. Cosmetic Uses. Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical pharmacy benefit.
Note: Examples of cosmetic uses include facial rhytides, frown lines, glabellar wrinkling, horizontal neck rhytides, mid and lower face and neck rejuvenation, platsymal bands, or rejuvenation of the periorbital region.

2. Gastroparesis. The ACG issued clinical guidelines on the management of gastroparesis (2013).[34] ACG does not recommend the use of botulinum toxin injected into the pylorus as a treatment for gastroparesis. This is based on two double-blind, placebo-controlled studies which did show some improvement in gastric emptying, but no improvement in symptoms compared with placebo.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Botulinum Toxin – Daxxify Prior Authorization Policy
- Daxxify® (daxibotulinumtoxinA-lanm injection – Revance)

REVIEW DATE: 08/30/2023

OVERVIEW

Daxxify (daxibotulinumtoxinA-lanm), is indicated for the following uses:[1]
- **Cervical dystonia** in adults.

The medication labeling, like all other botulinum toxin products, state the potency units of Daxxify are specific to the preparation and test method utilized and not interchangeable with other preparations of other botulinum toxin products [Botox® (onabotulinumtoxinA), Xeomin® (incobotulinumtoxinA), Dysport® (abobotulinumtoxinA), Myobloc® (rimabotulinumtoxinB)]; therefore, units of biological activity of Daxxify cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific test method.[1] Daxxify does not contain any human serum albumin in its formulation. The labeling also indicates a warning for potential serious adverse reactions after administration of Daxxify for unapproved uses.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Daxxify. All approvals are provided for the duration noted below.

Prior Authorization and prescription benefit are not recommended for cosmetic conditions.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Daxxify is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Cervical Dystonia.** Approve for 1 year if the patient is ≥ 18 years of age.
Note: Cervical dystonia is also known as spasmodic or cervical torticollis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Daxxify is not recommended in the following situations:

4. **Cosmetic Uses.** Note: Examples of cosmetic uses include facial rhytides, frown lines, glabellar wrinkling, horizontal neck rhytides, mid and lower face and neck rejuvenation, platsymal bands, or rejuvenation of the periorbital region. Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical pharmacy benefit.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

39. Daxxify® injection [prescribing information]. Newark, CA: Revance; August 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Botulinum Toxin – Dysport Prior Authorization Policy
- Dysport® (abobotulinumtoxinA injection – Ipsen/Galderma)

REVIEW DATE: 10/11/2023

OVERVIEW

Dysport (abobotulinumtoxinA) is indicated for the following uses:[1]
- **Cervical dystonia** in adults.
- **Spasticity** in patients ≥ 2 years of age.

Other Uses with Supportive Evidence

Botulinum toxins have been studied in a variety of indications outside of FDA-approved uses. Literature is available to support use of Dysport in the following conditions:
- **Anal Fissure:** There is an extensive amount of data from open-label studies; randomized, placebo-controlled trials; and randomized, comparative trials supporting the efficacy of botulinum toxin A in the treatment of anal fissures.[2-4] Injection of botulinum toxin allows healing in approximately 60% to 80% of anal fissures.[5] There is no consensus on the dose, site of injection, or number of injections. Botulinum toxin A has been shown to be more effective than topical nitroglycerin but less effective than surgery in inducing and maintaining fissure healing.[6] The American College of Gastroenterology clinical guideline for the management of benign anorectal disorders (2021) suggests that botulinum toxin A injections may be attempted for patients in whom calcium channel blockers fail or as an alternative option to calcium channel blockers (conditional recommendation; quality of evidence low).[4]
- **Blepharospasm:** Dysport has demonstrated efficacy in clinical trials in patients with blepharospasm.[7,8] American Academy of Neurology (AAN) guidelines (2016, reaffirmed 2022) support the use of Dysport for blepharospasm with a Level C recommendation ("possibly effective").[9]
- **Hemifacial Spasm:** Per the AAN, botulinum toxin (formulation not specified) may be considered in hemifacial spasm (Level C).[13] Data with Botox and Dysport are cited in the recommendations regarding hemifacial spasm.
- **Sialorrhea, Chronic:** Botulinum toxin A has been studied in the treatment of sialorrhea associated with Parkinson's Disease, parkinsonian syndromes, cerebral palsy, head and neck carcinoma, neurodegenerative disease, stroke, and amyotrophic lateral sclerosis.[10-12] Data with Dysport come from two small controlled trials.[10,11]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Dysport. All approvals are provided for 1 year in duration.

Prescription benefit coverage is not recommended for cosmetic conditions.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Dysport is recommended in those who meet one of the following criteria:

FDA-Approved Indications

2. **Cervical Dystonia.** Approve for 1 year if the patient is ≥ 18 years of age.
   Note: Cervical dystonia is also referred to as spasmodic or cervical torticollis.

3. **Spasticity, Limb**. Approve for 1 year if the patient is ≥ 2 years of age.

Other Uses with Supportive Evidence

4. **Anal Fissure.** Approve for 1 year if the patient is ≥ 18 years of age.

5. **Blepharospasm**. Approve for 1 year if the patient is ≥ 18 years of age.
   Note: This includes blepharospasm associated with dystonia, benign essential blepharospasm, seventh (VII) nerve disorders.

6. **Hemifacial Spasm**. Approve for 1 year if the patient is ≥ 18 years of age.

7. **Sialorrhea, Chronic.** Approve for 1 year if the patient is ≥ 18 years of age.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Dysport is not recommended in the following situations:

6. **Cosmetic Uses.** Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical pharmacy benefit.
   Note: Examples of cosmetic uses include facial rhytides, frown lines, glabellar wrinkling, horizontal neck rhytides, mid and lower face and neck rejuvenation, platsymal bands, or rejuvenation of the periorbital region.

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Botulinum Toxins – Myobloc Prior Authorization Policy
- Myobloc® (rimabotulinumtoxinB injection – Solstice Neurosciences)

REVIEW DATE: 01/11/2023

OVERVIEW

Myobloc (rimabotulinumtoxinB) is indicated for the following uses:[1]
- **Cervical Dystonia** in adults.
- **Sialorrhea, chronic** in adults.

Other Uses with Supportive Evidence

Spasticity, Upper Limb: In 2016 American Academy of Neurology guidelines (reaffirmed 2022), Myobloc is supported for use in upper limb spasticity (Level B; probably effective).[2] Of note, evidence is insufficient for Myobloc in the setting of lower limb spasticity (Level U).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Myobloc. All approvals are provided for the duration noted below.

Prior Authorization and prescription benefit coverage are not recommended for cosmetic conditions.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Myobloc is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Cervical Dystonia.** Approve for 1 year if the patient is ≥ 18 years of age.

2. **Sialorrhea, Chronic.** Approve for 1 year if the patient is ≥ 18 years of age.

Other Uses with Supportive Evidence

3. **Spasticity, Upper Limb.** Approve for 1 year if the patient is ≥ 18 years of age.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Myobloc is not recommended in the following situations:

1. **Cosmetic Uses.** Note: Examples of cosmetic uses include facial rhytides, frown lines, glabellar wrinkling, horizontal neck rhytides, mid and lower face and neck rejuvenation, platysmal bands, or rejuvenation of the periorbital region. Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical pharmacy benefit.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Botulinum Toxins – Xeomin Prior Authorization Policy
- Xeomin® (incobotulinumtoxinA injection – Merz)

REVIEW DATE: 10/11/2023

OVERVIEW

Xeomin (incobotulinumtoxinA) is indicated for the following uses:[1]
- **Blepharospasm** in adults.
- **Cervical dystonia** in adults.
- **Sialorrhea**, chronic, in patients ≥ 2 years of age.
- **Upper limb spasticity**:
  - In adults.
  - In pediatric patients ≥ 2 years of age, excluding spasticity caused by cerebral palsy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Xeomin. All approvals are provided for the duration noted below.

Prescription benefit coverage is not recommended for cosmetic conditions.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xeomin is recommended in those who meet one of the following criteria:

FDA-Approved Indications

8. **Blepharospasm**. Approve for 1 year if the patient is ≥ 18 years of age. Note: This includes blepharospasm associated with dystonia, benign essential blepharospasm, seventh (VII) nerve disorders.

9. **Cervical Dystonia.** Approve for 1 year if the patient is ≥ 18 years of age. Note: Cervical dystonia is also known as spasmodic or cervical torticollis.

10. **Sialorrhea, Chronic.** Approve for 1 year if the patient is ≥ 2 years of age.

11. **Spasticity, Upper Limb.** Approve for 1 year if the patient is ≥ 2 years of age.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xeomin is not recommended in the following situations:

7.

8. **Cosmetic Uses**. Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical pharmacy benefit.

Note: Examples of cosmetic uses include facial rhytides, frown lines, glabellar wrinkling, horizontal neck rhytides, mid and lower face and neck rejuvenation, platsymal bands, or rejuvenation of the periorbital region.

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

53. Xeomin® injection [prescribing information]. Raleigh, NC and Franksville, WI: Merz; August 2021.

PRIOR AUTHORIZATION POLICY

POLICY: Cardiology – Camzyos Prior Authorization Policy
- Camzyos™ (mavacamten capsules – MyoKardia/Bristol Myers Squibb)

REVIEW DATE: 05/17/2023

OVERVIEW

Camzyos, a cardiac myosin inhibitor, is indicated for the treatment of symptomatic New York Heart Association Class (NYHA) II to III **obstructive hypertrophic cardiomyopathy** in adults to improve functional capacity and symptoms.

Disease Overview

Hypertrophic cardiomyopathy is a complex myocardial disorder in which the walls of the heart muscle, more specifically the left ventricle, are thickened or hypertrophied.[2-5] The condition is inherited in an autosomal dominant pattern. The estimated prevalence is one in 200 to 500 adults. Patients of any age can be impacted. However, many patients may be undiagnosed or be asymptomatic. Diagnoses is usually by echocardiographic or magnetic resonance imaging which reveals a hypertrophied, nondilated left ventricle without another identifiable cardiac, systemic, metabolic or syndromic disease. The left ventricle becomes stiff, which makes it more difficult for the heart to normally expand and fill with blood. The amount of blood that the left ventricle can hold and pump throughout the body is reduced; the hypertrophied heart muscle may also pump with too much force. Many patients with hypertrophic cardiomyopathy have obstructive disease in which the path for blood flow out of the heart can narrow and the output to the rest of the body may be restricted which is referred to as left ventricular outflow tract obstruction. This forces the heart to pump harder to overcome the obstructive forces. Symptoms that are commonly present with hypertrophic cardiomyopathy include shortness of breath, palpitations, light headedness, chest pain, fatigue, and exercise intolerance. Many patients have heart failure, as well as atrial fibrillation or other ventricular arrhythmias. Sudden death may also result. Hypertrophic cardiomyopathy is due to enhanced interactions between two cardiac proteins, actin and myosin. Camzyos works by reducing the number of intersections formed between actin and myosin which leads to more optimized heart relaxation and filling; lessened heart muscle workload during contractions; and improved efficiency in energy utilized for each heartbeat. Before approval of Camzyos, treatment for obstructive hypertrophic cardiomyopathy focused on symptomatic relief with medications such as beta blockers, non-dihydropyridine calcium channel blockers (CCBs), and disopyramide. Septal reduction therapy is an option.

Clinical Efficacy

EXPLORER-HCM was a randomized, double-blind, placebo-controlled, parallel-group trial that evaluated Camzyos in over 250 patients with symptomatic NYHA Class II or III obstructive hypertrophic cardiomyopathy.[1,2] Patients had a left ventricular ejection fraction ≥ 55% and a left ventricular outflow tract peak gradient ≥ 50 mmHg (at rest or with provocation [Valsalva maneuver or post exercise]). Unexplained left ventricular hypertrophy was present with maximal left ventricular wall thickness of ≥ 15 mm or ≥ 13 mm if the patient had familial hypertrophic cardiomyopathy.[2] Approximately 75% of patients were receiving beta blockers and 17% of patients were on CCBs for symptoms. The primary composite functional endpoint, evaluated at 30 weeks, was defined as the proportion of patients who achieved either improvement of mixed venous oxygen tension/peak oxygen consumption (pVO_2) by ≥ 1.5 mL/kg/min plus improvement in NYHA class by at least one or improvement of pVO_2 by ≥ 3.0 mL/kg/min plus no worsening in NYHA class. A greater proportion of patients receiving Camzyos met this composite endpoint compared with patients given placebo (37% vs. 17%, respectively; P = 0.0005). Regarding secondary

endpoints, Camzyos led to greater improvements compared with placebo in measures assessing left ventricular outflow tract (LVOT) obstruction, functional capacity, and health status. These parameters were assessed by change from baseline through Week 30 in post-exercise LVOT peak gradient, change in pVO_2, proportion of patients with improvement in NYHA class, Kansas City Cardiomyopathy Questionnaire-23 (KCCQ-23) Clinical Summary Score (CSS), and Hypertrophic Cardiomyopathy Symptoms Questionnaire (HCMSQ) Shortness of Breath domain score.[1,2] At Week 30, there were also reductions in N-terminal pro B-type natriuretic peptide and high-sensitivity cardiac troponin I levels from baseline.[2] Other data are also available.[6]

Guidelines

Guidelines have not incorporated Camzyos.

- **Hypertrophic Cardiomyopathy:** In 2020, the American Heart Association and the American College of Cardiology published guidelines for the diagnosis and treatment of patients with hypertrophic cardiomyopathy.[7] For symptomatic patients with obstructive hypertrophic cardiomyopathy attributable to LVOT obstruction, nonvasodilating beta blockers are recommended to be titrated to effectiveness or maximally tolerated doses. In patients for whom beta blockers are not effective or not tolerated, substitution with nondihydropyridine CCBs (e.g., verapamil, diltiazem) is recommended. If the patient continues to have persistent severe symptoms despite beta blocker therapy or CCBs, either adding disopyramide in combination with one of the other drugs is recommended. Also, septal reduction therapy, performed at experienced centers, is an option for selected patients. One of the other key steps in managing symptomatic, obstructive hypertrophic cardiomyopathy is to eliminate medication that may promote outflow tract obstruction like pure vasodilators (e.g., dihydropyridine CCBs, angiotensin converting enzyme inhibitors, angiotensin receptor blockers) and high-dose diuretics. Low-dose diuretics, when added to other first-line medications, may be useful for patients with persistent dyspnea or congestive symptoms.

Safety

Camzyos has a Boxed Warning regarding the risk of heart failure.[1] The agent may cause heart failure due to systolic dysfunction. Echocardiogram assessment of left ventricular ejection fraction is required before and during Camzyos use. Initiation in patients with a left ventricular ejection fraction < 55% is not recommended. Therapy should be interrupted if left ventricular ejection fraction is less than 50% or if worsening clinical status occurs. Certain cytochrome P450 inhibitors and inducers are contraindicated in patients receiving Camzyos due to an increased risk of heart failure. Camzyos is available only through a restricted program called the Camzyos Risk Evaluation and Mitigation Strategy (REMS) program. Notable requirements include the following:

- Prescribers must be certified by enrolling in the Camzyos REMS program.
- Patients must enroll in the Camzyos REMS program and comply with ongoing monitoring requirements.
- Pharmacies must be certified by enrolling in the Camzyos REMS program and must only dispense to patients who are authorized to receive Camzyos.
- Wholesalers and distributors must only distribute the medication to certified pharmacies.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Camzyos. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Camzyos as well as the monitoring required for adverse events and long-term efficacy, approval requires Camzyos to be prescribed by a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Camzyos is recommended in those who meet the following criteria:

FDA-Approved Indication

10. Obstructive Hypertrophic Cardiomyopathy. Approve for the duration noted below if the patient meets ONE of the following criteria (A or B):
- **A)** Initial Therapy. Approve for 8 months if the patient meets the following criteria (i, ii, iii, iv, v, and vi):
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** Patient meets both of the following (a and b):
    - **a)** Patient has at least one symptom associated with obstructive hypertrophic cardiomyopathy; AND
      Note: Examples of symptoms include shortness of breath, chest pain, lightheadedness, fainting, fatigue, and reduced ability to perform physical exercise.
    - **b)** Patient has New York Heart Association Class II or III symptoms of heart failure; AND
      Note: Class II signifies mild symptoms with moderate physical activity and some exercise limitations whereas Class III denotes noticeable symptoms with minimal physical activity and patients are only comfortable at rest.
  - **iii.** Patient with left ventricular hypertrophy meets one of the following (a or b):
    - **a)** Patient has maximal left ventricular wall thickness ≥ 15 mm; OR
    - **b)** Patient has familial hypertrophic cardiomyopathy with a maximal left ventricular wall thickness ≥ 13 mm; AND
  - **iv.** Patient has a peak left ventricular outflow tract gradient ≥ 50 mmHg (at rest or after provocation [Valsalva maneuver or post exercise]); AND
  - **v.** Patient has a left ventricular ejection fraction of ≥ 55%; AND
  - **vi.** The medication is prescribed by a cardiologist; OR
- **B)** Patient Currently Receiving Camzyos. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, iv, v and vi):
  - **i.** Patient has been established on therapy for at least 8 months; AND
    Note: A patient who has received < 8 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).
  - **ii.** Patient is ≥ 18 years of age; AND
  - **iii.** Patient meets both of the following (a and b):
    - **a)** Currently or prior to starting therapy, patient has or has experienced at least one symptom associated with obstructive hypertrophic cardiomyopathy; AND
      Note: Examples of symptoms include shortness of breath, chest pain, lightheadedness, fainting, fatigue, and reduced ability to perform physical exercise.
    - **b)** Currently or prior to starting therapy, patient is in or was in New York Heart Association Class II or III heart failure; AND
      Note: Class II signifies mild symptoms with moderate physical activity and some exercise limitations whereas Class III denotes noticeable symptoms with minimal physical activity and patients are only comfortable at rest.
  - **iv.** Patient has a current left ventricular ejection fraction of ≥ 50%; AND
  - **v.** Patient meets at least one of the following (a or b):
    - **a)** Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR

Note: Examples include improved peak oxygen consumption/mixed venous oxygen tension; decreases in left ventricular outflow tract gradient; reductions in N-terminal pro-B-type natriuretic peptide levels; decreased high-sensitivity cardiac troponin I levels; reduced ventricular mass index; and/or a reduction in maximum left atrial volume index.

b) Patient experienced stabilization or improvement in at least one symptom related to obstructive hypertrophic cardiomyopathy; AND

Note: Examples of symptoms include shortness of breath, chest pain, lightheadedness, fainting, fatigue, ability to perform physical exercise, and/or favorable changes in the Kansas City Cardiomyopathy Questionnaire-23 (KCCQ-23) Clinical Summary Score (CSS) or Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ) Shortness of Breath domain scores.

vi. The medication is prescribed by a cardiologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Camzyos is not recommended in the following situations:

46. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

138. Camzyos™ capsules [prescribing information]. Princeton, NJ: MyoKardia/Bristol Myers Squibb; September 2022.
139. Olivotto I, Oreziak A, Barriales-Villa R, et al, for the EXPLORER-HCM study investigators. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2020;396(10253):759-769.
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PRIOR AUTHORIZATION POLICY

POLICY: Cardiology – Corlanor Prior Authorization Policy
- Corlanor® (ivabradine tablets and oral solution – Amgen)

REVIEW DATE: 06/14/2023

OVERVIEW

Corlanor, a hyperpolarization-activated cyclic nucleotide-gated channel blocker, is indicated for the following uses:[1]

- **Heart failure, in adults**, to reduce the risk of hospitalization for worsening of the disease in those with stable, symptomatic chronic heart failure with left ventricular ejection fraction (LVEF) ≤ 35%, who are in sinus rhythm with a resting heart rate ≥ 70 beats per minute (bpm) and either are receiving maximally tolerated doses of beta blockers or have a contraindication to beta blocker use.
- **Heart failure, in pediatric patients ≥ 6 months and older**, for treatment of stable symptomatic disease due to dilated cardiomyopathy, among those who are in sinus rhythm with an elevated heart rate.

Data are available with Corlanor that note improvement in symptoms and increased exercise performance in patients with inappropriate sinus tachycardia, defined as a sinus heart rate > 100 bpm at rest (with a mean 24-hour heart rate > 90 bpm not due to primary causes) which is generally is associated with distressing symptoms such as palpitations, weakness, dizziness and syncope.[2-9] Beta blockers have also been used for this condition. Limited data are available for other treatments that have been used and/or effectiveness have not been established (e.g., beta blockers, fludrocortisone, volume expansion, clonidine, and erythropoietin).

Guidelines

A few guidelines have recommendations that involve Corlanor.

- **Heart Failure:** The American Heart Association/American College of Cardiology/Heart Failure Society of America published guidelines in 2022 for the management of heart failure.[10] For patients with symptomatic (New York Heart Association Class II to III) stable chronic heart failure with reduced ejection fraction (LVEF ≤ 35%) who are receiving guideline-directed medical therapy, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of ≥ 70 beats per minute at rest, Corlanor can be beneficial to reduce heart failure hospitalizations and cardiovascular death.
- **Inappropriate Sinus Tachycardia:** The 2015 Heart Rhythm Society Expert Consensus Statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope state that Corlanor can be useful for treating patients with inappropriate sinus tachycardia.[2] Additionally, the 2015 American College of Cardiology, American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society also state that Corlanor is reasonable for ongoing management in patients with symptomatic inappropriate sinus tachycardia (class IIa recommendation).[3] Beta blockers may be considered for ongoing management in patients with symptomatic inappropriate sinus tachycardia (class IIb recommendation). Also, the guidelines state that the combination of beta blockers and Corlanor may be considered for the ongoing management of patients with inappropriate sinus tachycardia (class IIb recommendation). Because of the specialized skills required for evaluation and diagnosis of patients treated with Corlanor as well as the monitoring required for adverse events and long-term efficacy, approval requires Corlanor to be prescribed by or in consultation with a physician who specializes in the condition being treated.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Corlanor. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Corlanor is recommended in those who meet one of the following criteria:

FDA-Approved Indications

11. Heart Failure. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
- **C)** Patient is ≥ 18 years of age; AND
- **D)** Patient has a left ventricular ejection fraction (LVEF) ≤ 35% currently or prior to initiation of Corlanor therapy; AND
- **E)** Patient is in normal sinus rhythm or sinus tachycardia with a resting heart rate of ≥ 70 beats per minute; AND
- **F)** Patient meets one of the following (i or ii):
  - **i.** Patient has tried or is currently receiving one beta blocker for heart failure treatment; OR
    Note: Examples of beta blockers are metoprolol succinate sustained-release, carvedilol, bisoprolol, and Coreg CR (carvedilol extended-release capsules).
  - **ii.** Patient has a contraindication to use of beta blocker therapy; AND
    Note: Examples that are contraindications to use of beta blockers are bronchospastic disease such as chronic obstructive pulmonary disease and asthma, severe hypotension or bradycardia.
- **G)** Medication is prescribed by, or in consultation with, a cardiologist.

2. Heart Failure due to Dilated Cardiomyopathy in Pediatric Patients. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient is < 18 years of age; AND
- **B)** Medication is prescribed by, or in consultation with, a cardiologist.

Other Uses with Supportive Evidence

3. Inappropriate Sinus Tachycardia. Approve for 1 year if the medication is prescribed by, or in consultation with, a cardiologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Corlanor is recommended in those who meet the following criteria:

47. Stable Angina Pectoris, in Patients Without Chronic Heart Failure. Corlanor has been studied as a treatment for stable angina pectoris but further data are needed.[11-13] US guidelines addressing stable angina do not include Corlanor.[14,15]

48. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Cardiology – Lodoco Prior Authorization Policy
- Lodoco® (colchicine 0.5 mg tablets – Agepha)

REVIEW DATE: 08/30/2023

OVERVIEW

Lodoco, an alkaloid, is indicated to reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, and cardiovascular (CV) death in adults with established atherosclerotic disease or with multiple risk factors for CV disease.[1] The safety and effectiveness have not been established in pediatric patients.

Clinical Efficacy

The efficacy of Lodoco was evaluated in one, double-blind, placebo-controlled, event-driven, investigator-initiated, pivotal study called LoDoCo2 involving 5,522 adults with chronic stable coronary disease who received Lodoco 0.5 mg once daily or matching placebo.[1,2] The mean patient age was 66 years; only 15% of patients were female. Patients had an estimated glomerular filtration rate ≥ 50 mL/min. An acute coronary syndrome event had occurred previously in 84% of patients. Most patients were also receiving standard of care therapy for secondary prevention of CV events. Examples of medications utilized for chronic coronary disease included antiplatelet agents or an anticoagulant (99.7%), a lipid-lowering agent (96.6% [mostly statins]), a renin-angiotensin system inhibitor (71.7%), and beta-blockers (62.1%). The median time on study medication was 28.6 months. A primary endpoint event (a composite of CV death, MI, ischemic stroke, or ischemia-driven coronary revascularization) occurred in 6.8% of patients randomized to Lodoco vs. 9.6% of patients receiving placebo (hazard ratio 0.69; $P < 0.001$).

Guidelines

Guidelines for the management of patients with chronic coronary disease from the American Heart Association and the American College of Cardiology (2023) state that in patients with chronic coronary disease, the addition of colchicine for secondary prevention may be considered to reduce recurrent atherosclerotic cardiovascular disease events (Class of Recommendation: 2b [weak] {benefit ≥ risk}; Level of Evidence: randomized).[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lodoco. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lodoco is recommended in those who meet the following criteria:

FDA-Approved Indication

32. Atherosclerotic Disease. Approve for 1 year if the patient meets the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has had one of the following conditions or diagnoses (i, ii, iii, iv, v, or vi):
  - **i.** A previous myocardial infarction or a history of an acute coronary syndrome; OR
  - **ii.** Angina (stable or unstable); OR
  - **iii.** A past of stroke or transient ischemic attack; OR
  - **iv.** Coronary artery disease; OR
  - **v.** Peripheral arterial disease; OR
  - **vi.** Patient has undergone a coronary or other arterial revascularization procedure in the past; AND
    Note: Examples include coronary artery bypass graft surgery, percutaneous coronary intervention, angioplasty, and coronary stent procedures.
- **C)** Lodoco is being added onto other background regimens of other atherosclerotic disease medications according to the prescriber; AND
  Note: Examples of medications recommended in guideline-directed therapy for patients with atherosclerotic disease can include aspirin, antiplatelet agents (e.g., clopidogrel, Brilinta [ticagrelor tablets]), anticoagulants, lipid-lowering agents (e.g., statins such as atorvastatin and rosuvastatin), beta blockers, angiotensin-converting enzyme inhibitors, and/or angiotensin receptor blockers.
- **D)** Patient does not have severe hepatic impairment according to the prescriber; AND
- **E)** Patient has a creatinine clearance ≥ 50 mL/min.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lodoco is not recommended in the following situations:

28. Primary Prevention of Cardiovascular Events. Guidelines for the primary prevention of cardiovascular disease do not currently address Lodoco.[4] Most patients in the pivotal trial with Lodoco had past cardiovascular events or had undergone a coronary or other arterial revascularization procedure in the past.[2]

29. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Cardiology – Zontivity Prior Authorization Policy
- Zontivity® (vorapaxar tablets – Wraser)

REVIEW DATE: 11/15/2023

OVERVIEW

Zontivity, a protease-activated receptor-1 antagonist, is indicated for the reduction of thrombotic cardiovascular (CV) events in patients with **a history of myocardial infarction (MI) or with peripheral arterial disease (PAD)**.[1] The agent has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization.

Studies involving Zontivity involved adding the agent to aspirin and/or clopidogrel. Use Zontivity with aspirin and/or clopidogrel according to indicated uses or the standard of care. The clinical use of Zontivity with other antiplatelet medications is limited, as well as data involving Zontivity as the only antiplatelet agent. In a subgroup analysis of the pivotal data, patients weighing < 60 kg who received Zontivity did not have a favorable outcome regarding the primary composite endpoint of CV death, MI, stroke, or urgent coronary revascularization.[1,2]

Guidelines

The guidelines for the management of patients with chronic coronary disease (2023) from the American Heart Association and the American College of Cardiology address Zontivity.[3] It is noted that in the TRAP 2P TIMI 50 trial, at a mean follow-up of 3 years, patients with a history of MI, ischemic stroke, or PAD randomized to either Zontivity, on a background of aspirin therapy, had a reduced number of ischemic events or died from common from CV causes after 3 years compared with placebo. However, patients experienced more major and intracranial bleeding.

Safety

Zontivity has a Boxed Warning regarding the risk of bleeding.[1] Zontivity is contraindicated in patients with a history of stroke, transient ischemic attack, or intracranial hemorrhage (ICH). Antiplatelet medications, including Zontivity, increase the risk of bleeding, including ICH and fatal bleeding.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zontivity. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zontivity is recommended in patients who meet the following criteria:

FDA-Approved Indication

12. **Patient with a Previous Myocardial Infarction (MI) or Peripheral Arterial Disease (PAD).** Approve for 1 year if the patient meets the following (A, B, and C):
    O) Patient weighs ≥ 60 kg; AND
    P) Patient is receiving Zontivity in combination with aspirin and/or clopidogrel; AND
    Q) Patient has been determined by the prescriber to be at high risk for future thrombotic events.
    Note: Examples of high risk include that the patient has experienced multiple myocardial infarctions, has undergone many urgent coronary revascularization procedures, has had placement of coronary artery stents, or the patient has other concomitant diseases that increase cardiovascular risk such as diabetes.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zontivity is not recommended in the following situations:

49. **Acute Coronary Syndrome (ACS) that Occurred Recently (within < 14 days).** In the TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in acute coronary syndrome) study, adding Zontivity to standard therapy in those who experienced an ACS increased the risk of major bleeding and did not result in clinical benefits.

50. **Patient with a Prior History of Stroke, Transient Ischemic Attack (TIA), or Intracranial Hemorrhage (ICH).** Zontivity is contraindicated for use in patients with a of stroke, TIA, or ICH due to an increased risk of ICH in this population.

51. **Concurrent Use of Effient (prasugrel tablets) or Brilinta (ticagrelor tablets).** There is limited clinical experience involving use of Zontivity with antiplatelet agents (e.g., Effient, Brilinta) other than aspirin and/or clopidogrel.

52. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Chelating Agents – Chemet Prior Authorization Policy
- Chemet® (succimer capsules – Lannett/Recordati Rare Diseases)

REVIEW DATE: 04/26/2023

OVERVIEW

Chemet, a heavy metal chelator, is indicated for the treatment of **lead poisoning** in pediatric patients with blood lead levels > 45 mcg/dL.[1] Chemet is not indicated for prophylaxis of lead poisoning in a lead-containing environment; the use of Chemet should be accompanied by identification and removal of the source of the lead exposure. Safety and efficacy of Chemet in children < 12 months of age have not been established. The course of therapy is 19 days; if indicated, a repeat course may be given with a minimum of 2 weeks between courses, unless blood lead levels indicate the need for more prompt treatment. The chemical name for Chemet is *meso* 2,3-dimercaptosuccinic acid (DMSA).

Disease Overview

Lead, mercury, arsenic, and iron account for most cases of diagnosed heavy metal poisoning in the US.[2] Most cases of lead poisoning are in children who swallow lead-based paint in homes or toys; other causes include water carried through pipes made of lead or containing lead solder. Children are especially susceptible to the toxic effects of lead, which may affect the developing brain and nervous system, potentially causing lower IQs, learning difficulties, hearing loss, and behavior difficulties. In adults, lead poisoning can cause high blood pressure and kidney damage.

Other Uses with Supportive Evidence

Arsenic is a naturally-occurring substance; in some areas of the world, low-level arsenic exposure occurs because of the presence of arsenic in ground water.[2] Accidental poisoning accounts for the majority of acute arsenic toxicity.[3] The Agency for Toxic Substances and Disease Registry (ATSDR) states that patients with severe arsenic poisoning must be hospitalized.[7] Chelation therapy can curtail the distribution of arsenic in the body and reduce the body burden. Oral chelators, such as Chemet, have been used with success. There are case reports to support the use of DMSA in acute arsenic poisoning.[3,8] The patients' clinical status improved with DMSA therapy and urine arsenic levels decreased with therapy.

Mercury poisoning can result from vapor inhalation, mercury ingestion, mercury injection, and absorption of mercury through the skin.[5] Symptoms of mercury poisoning depends on the type of mercury exposure and severity of exposure: organic mercury (antiseptics, bactericidals, fungicides, insecticides), inorganic mercury (chemical laboratory work, disinfectants, explosives, fur hat processing), and elemental mercury (thermometers, batteries, dental amalgams, fluorescent lamps). The ATSDR notes that patients with serious mercury exposure must be hospitalized.[9] Chelation should be considered for any symptomatic patient with a clear history of acute elemental mercury exposure. The decision to chelate is less clear in asymptomatic patients with elevated urine mercury levels.[10] Oral chelators, such as Chemet, have been used successfully for the treatment of acute mercury intoxication/poisoning.[9] The World Health Organization (WHO) recommends that urine mercury concentration should not exceed 50 mcg/g creatinine.[11]

Several case reports have demonstrated the effectiveness of DMSA therapy for treatment of acute mercury poisoning.[12-15] All of the patients exhibited symptoms consistent with mercury poisoning and were treated in a hospital setting. DMSA therapy resulted in reduction of mercury levels and improved symptomatology.

Treatment Recommendations

Treatment of heavy metal poisoning includes removing the patient from the source of the metal and treating the patient's symptoms.[2] Diagnosis includes the patient's history, symptoms, and blood or urine tests.[2,4,5] Treatment of acute metal poisoning involves emergency care and generally requires the use of chelating agents, such as DMSA.[6] (Note: the chemical name, DMSA, will be used to describe the case reports in this document because it is unclear if the FDA-approved Chemet product was used).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Chemet. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Chemet as well as the monitoring required for adverse events, approval requires Chemet to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Chemet as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Chemet is recommended in those who meet one of the following criteria:

FDA-Approved Indication

13. **Acute Lead Poisoning.** Approve for 2 months if the patient meets the following criteria (A, B, C, and D):
    - **B)** Patient is between the age of 12 months and 18 years of age; AND
    - **C)** Prior to starting Chemet therapy, the patient's blood lead level was > 45 mcg/dL **[documentation required]**; AND
    - **D)** Chemet is being used for treatment of acute lead poisoning and not as prophylaxis against lead poisoning in a lead-containing environment; AND
    - **E)** The medication is prescribed by or in consultation with a professional experienced in the use of chelation therapy (e.g., a medical toxicologist or a poison control center specialist).

Other Uses with Supportive Evidence

14. **Acute Arsenic Intoxication/Poisoning.** Approve for 1 month if the patient meets the following criteria (A and B):
    - **A)** Patient was recently initiated on Chemet therapy in the hospital and further treatment is needed to finish the course of therapy; AND
    - **B)** The medication is prescribed by or in consultation with a professional experienced in the use of chelation therapy (e.g., a medical toxicologist or a poison control center specialist).

15. **Acute Mercury Intoxication/Poisoning.** Approve for 1 month if the patient meets the following criteria (A and B):
    - **A)** Patient was recently initiated on Chemet therapy in the hospital and further treatment is needed to finish the course of therapy; AND
    - **B)** The medication is prescribed by or in consultation with a professional experienced in the use of chelation therapy (e.g., a medical toxicologist or a poison control center specialist).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Chemet is not recommended in the following situations:

53. **Use of Chemet in Conjunction with other Chelators (e.g., calcium disodium versenate injection [$CaNa_2EDTA$], dimercaprol injection [British anti-Lewisite {BAL}]).**
    In patients with acute lead poisoning, data on the concomitant use of Chemet with $CaNa_2EDTA$ with or without BAL are not available and such use is not recommended.[1]

2. **Chelation of Heavy Metals to Treat Chronic Medical and/or Psychiatric Conditions.** Chelation of heavy metals has been advertised as a viable treatment for numerous conditions: treatment of intermittent claudication; treatment or management of symptoms of autism; prevention or cure of neurodegenerative conditions such as Alzheimer's disease; use in Parkinson's disease; treatment of macular degeneration.[2] There is no evidence to show that chelators work in these conditions. Furthermore, unapproved uses of chelation therapy have resulted in harm and even death. Chelation of heavy metals is also one of several popular interventions in children with autism spectrum disorders. The FDA notes chelation therapies for the treatment of autism to be associated with significant health risks and does not approve such use.[16]

3. **Chronic Arsenic Exposure.** Use of chelation therapy following chronic exposure to inorganic arsenic may accelerate metal excretion, but potential therapeutic efficacy in terms of decreased morbidity and mortality is largely unestablished.[17]

    In a prospective, randomized-controlled trial, 21 patients with chronic arsenicosis due to drinking arsenic-contaminated subsoil water were randomized to receive DMSA (1,400 mg/day or 100 mg/m^2 in four divided doses for 1 week and then 1,050 mg/day or 750 mg/m^2 in three divided doses for 2 weeks; repeat the regimen after 3 weeks) or placebo.[18] The patients had of drinking arsenic-contaminated water (50 mcg/L or $\geq$ 0.05 mg/L) for at least 2 years and exhibited clinical signs/symptoms of chronic arsenicosis. Similar improvement in the clinical score was observed in the DMSA and placebo groups. Furthermore, urinary arsenic excretion before treatment and at 48 hours and 72 hours post-treatment were similar between the two groups. The investigators concluded that DMSA did not result in clinical or biochemical benefit in patients with chronic arsenicosis.

    In another case report involving a 39 year old woman with arsenic poisoning (urine arsenic level was 2,000 mcg/L; normal level is < 10 mcg/L), DMSA 600 mg three times a day for 45 days did not significantly affect the clearance of arsenic or clinical outcome.[19] During the 45-day course, the patient stopped therapy for a total of 13 days (unknown reason).

4. **Chronic Mercury Exposure.** The American Academy of Pediatrics notes there is no scientific evidence behind the use of chelation therapy to improve nervous system symptoms of chronic mercury toxicity.[16] Use of chelation therapy following chronic exposure to inorganic mercury may accelerate metal excretion, but potential therapeutic efficacy in terms of decreased morbidity and mortality is largely unestablished.[17]

In a randomized, double-blind, parallel-group, placebo-controlled study in Sweden, 20 patients were randomized to receive DMSA 20 mg/kg/day in three divided doses or placebo for 14 days.[20] These patients experienced symptoms that were allegedly associated with amalgam fillings for at least 6 months. DMSA therapy resulted in increased urinary excretion of mercury and blood mercury levels were decreased. However, there were no statistically significant changes in any of the symptoms. The investigators concluded that although urinary excretion of mercury was increased during DMSA treatment, chelating therapy did not alleviate symptoms allegedly attributable to mercury from amalgam fillings.

Cao and colleagues reported the effects of Chemet in reducing blood mercury levels in children 12 to 33 months of age.[21] The original study was to evaluate the use of Chemet for lead poisoning; the investigators used the blood samples for the lead study and measured the mercury levels. Blood mercury concentrations were measured one week before randomization and treatment, at one week after treatment initiation, and after three courses of treatment. Mercury was not detected/quantified in any of the blood samples. At one week of treatment, organic mercury concentration decreased 8% in the Chemet group, but remained the same in the placebo group (P = 0.04). However, the investigators suggested that the difference was not due to a reduction in the Chemet group but rather, Chemet therapy prevented a rise in the blood mercury concentration as seen in the placebo group. Chemet therapy did not reverse the accumulation of organic mercury over multiple courses over 5 months.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Chelating Agents – Iron Chelators (Oral) Prior Authorization Policy
- Exjade® (deferasirox tablets for suspension – Novartis, generic)
- Ferriprox® (deferiprone tablets and oral solution – Chiesi, generic [tablets only])
- Jadenu® (deferasirox tablets – Novartis, generic)
- Jadenu® Sprinkle (deferasirox oral granules – Novartis, generic)

REVIEW DATE: 05/17/2023

OVERVIEW

Oral iron chelator products are indicated for the **treatment of iron overload** for specific conditions.[1-4]

Deferasirox products are indicated for the following uses:[1,2]
- **Chronic iron overload due to blood transfusions**, in patients ≥ 2 years of age.
- **Chronic iron overload in non-transfusion-dependent thalassemia syndromes**, in patients ≥ 10 years of age with a liver iron concentration of at least 5 mg of iron per gram of liver dry weight and a serum ferritin > 300 mcg/L.

Deferiprone tablets are indicated for the following uses:[3]
- **Transfusional iron overload with thalassemia syndromes**, in patients ≥ 8 years of age.
- **Transfusional iron overload with sickle cell disease or other anemias**, in patients ≥ 8 years of age.

Deferiprone solution is indicated for the following uses:[4]
- **Transfusional iron overload with thalassemia syndromes**, in patients ≥ 3 years of age.
- **Transfusional iron overload with sickle cell disease or other anemias**, in patients ≥ 3 years of age.

Disease Overview

Iron chelating therapy should be considered in all patients who require long-term blood transfusions.[5] Patients with sickle cell disease, myelodysplastic syndromes (MDS), thalassemia major, Diamond-Blackfan anemia, aplastic anemia, and other congenital and acquired forms of refractory anemia (e.g., hereditary hemochromatosis) may require regular blood transfusions and as a result may require iron chelating therapy. This is because the body does not have an efficient mechanism to excrete iron.[6] In patients requiring multiple blood transfusions, iron accumulates and is deposited into multiple organ systems. The long-term consequences of chronic iron overload include multiple organ dysfunction (e.g., heart, liver) and/or organ failure. Iron chelation therapy is necessary to prevent organ failure and decrease mortality.

Guidelines

- **Thalassemia Syndromes:** The Thalassemia International Federation published guidelines (2021) for transfusion-dependent thalassemia.[7] Initiation of an iron chelator generally starts after 10 to 20 infusions or when serum ferritin level is > 1,000 mcg/L. Recommendations advise use based on patient characteristics and FDA-approved indications and also advocate for switching, rotating, and combing chelator regimens as needed to control iron balance or distribution.
  The American Heart Association (AHA) published a consensus statement (2013) on cardiovascular function and treatment in patients with β-thalassemia major.[8] Deferasirox, deferiprone, and

deferoxamine (injectable iron chelator) are recommended chelating treatments. The AHA advises the use of Ferriprox monotherapy in patients with cardiac siderosis, patients with reduced left ventricular ejection fraction (LVEF), or asymptomatic left ventricular dysfunction. Exjade and Jadenu monotherapy can be used in patients with detectable cardiac iron levels and normal cardiac function. However, Exjade and Jadenu are not recommended as first-choice treatment for cardiac siderosis with cardiac iron (T2*) < 6 ms or in patients with reduced LVEF.

- **MDS:** The National Comprehensive Cancer Network (NCCN) guidelines for MDS (version 1.2023 – September 12, 2022) have recommendations for the management of iron overload.[9] NCCN advises consideration of deferasirox or deferoxamine (injectable iron chelator) to decrease iron overload (aiming for target ferritin level < 1,000 mcg/mL) in specific patients with MDS or who are potential transplant candidates. The guidelines note that deferiprone is available; however, controversy remains regarding the use of this agent for MDS due to the Boxed Warning for agranulocytosis.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of oral iron chelator products. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with oral iron chelator products as well as the monitoring required for adverse events and long-term efficacy, initial approval requires oral iron chelator products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of oral iron chelator products as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of **deferasirox products** is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Iron Overload, Chronic – Transfusion-Related.** Approve for 1 year if the patient meets ONE of the following criteria (A or B):
   - **A)** Initial Therapy. Approve if the patient meets ALL of the following criteria (i, ii, and iii):
     - **i.** Patient is receiving blood transfusions at regular intervals for a chronic condition; AND
       Note: Examples of chronic conditions include thalassemia syndromes, myelodysplastic syndrome, chronic anemia, and sickle cell disease.
     - **ii.** Prior to starting chelating therapy, serum ferritin level was > 1,000 mcg/L **[documentation required]**; AND
     - **iii.** The medication is prescribed by or in consultation with a hematologist.
   - **B)** Patient is Currently Receiving a Deferasirox Product. Approve if the patient is benefiting from therapy, as confirmed by the prescriber.
     Note: Examples of benefit from therapy include reduction in serum ferritin levels, stable disease, and reduced organ iron load.
2. **Iron Overload, Chronic – Non-Transfusion-Dependent Thalassemia Syndromes.** Approve for 1 year if the patient meets ONE of the following criteria (A or B):
   - **A)** Initial Therapy. Approve if the patient meets BOTH of the following criteria (i and ii):

i. Prior to starting chelating therapy, serum ferritin level was > 300 mcg/L **[documentation required]**; AND

ii. The medication is prescribed by or in consultation with a hematologist.

B) Patient is Currently Receiving a Deferasirox Product. Approve if the patient is benefiting from therapy, as confirmed by the prescriber.

Note: Examples of benefit from therapy include reduction in serum ferritin levels, stable disease, and reduced organ iron load.

II. Coverage of **deferiprone products** is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Iron Overload, Chronic – Transfusion-Related Due to Thalassemia Syndromes.** Approve for 1 year if the patient meets ONE of the following criteria (A or B):

2. Initial Therapy. Approve if the patient meets BOTH of the following criteria (i and ii):

i. Prior to starting chelating therapy, serum ferritin level was > 1,000 mcg/L **[documentation required]**; AND

ii. The medication is prescribed by or in consultation with a hematologist.

3. Patient is Currently Receiving a Deferiprone Product. Approve if the patient is benefiting from therapy, as confirmed by the prescriber.

Note: Examples of benefit from therapy include reduction in serum ferritin levels, stable disease, and reduced organ iron load.

2. **Iron Overload, Chronic – Transfusion-Related Due to Sickle Cell Disease or Other Anemias.** Approve for 1 year if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve if the patient meets BOTH of the following criteria (i and ii):

i. Prior to starting chelating therapy, serum ferritin level was > 1,000 mcg/L **[documentation required]**; AND

ii. The medication is prescribed by or in consultation with a hematologist.

B) Patient is Currently Receiving a Deferiprone Product. Approve if the patient is benefiting from therapy, as confirmed by the prescriber.

Note: Examples of benefit from therapy include reduction in serum ferritin levels, stable disease, and reduced organ iron load.

Other Uses with Supportive Evidence

3. **Iron Overload, Chronic – Non-Transfusion-Dependent Thalassemia Syndromes.** Approve for 1 year if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve if the patient meets BOTH of the following criteria (i and ii):

i. Prior to starting chelating therapy, serum ferritin level was > 300 mcg/L **[documentation required]**; AND

ii. The medication is prescribed by or in consultation with a hematologist.

B) Patient is Currently Receiving a Deferiprone Product. Approve if the patient is benefiting from therapy, as confirmed by the prescriber.

Note: Examples of benefit from therapy include reduction in serum ferritin levels, stable disease, and reduced organ iron load.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of oral iron chelator products is not recommended in the following situations:

30. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

117. Exjade® tablets for suspension [prescribing information]. East Hanover, NJ: Novartis; July 2020.
118. Jadenu® tablets and Jadenu® Sprinkle oral granules [prescribing information]. East Hanover, NJ: Novartis; July 2020.
119. Ferriprox® tablets [prescribing information]. Cary, NC: Chiesi; April 2021.
120. Ferriprox® oral solution [prescribing information]. Cary, NC: Chiesi; November 2021.
121. Brittenham GM. Iron-chelating therapy for transfusional iron overload. *N Engl J Med*. 2011;364:146-156.
122. Palmer WC, Vishnu P, Sanchez W, et al. Diagnosis and Management of Genetic Iron Overload Disorders. *J Gen Intern Med*. 2018 Dec;33(12):2230-2236.
123. Farmakis D, Porter J, Taher A, et al. 2021 Thalassaemia International Federation Guidelines for the Management of Transfusion-dependent Thalassemia. *Hemasphere*. 2022;6(8):e732. Published 2022 Jul 29.
124. Pennell DJ, Udelson JE, Arai AE, et al. Cardiovascular function and treatment in β-thalassemia major. A consensus statement from the American Heart Association. *Circulation*. 2013;128:281-308.
125. The NCCN Myelodysplastic Syndrome Clinical Practice Guidelines in Oncology (version 1.2023 – September 12, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 15, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Chelating Agents – Penicillamine Products Prior Authorization with Step Therapy Policy
- Cuprimine® (penicillamine capsules – Valeant, generic)
- Depen® (penicillamine tablets – Meda, generic)

REVIEW DATE: 11/15/2023

OVERVIEW

Penicillamine products (capsules [Cuprimine, generic] and tablets [Depen, generic]) are chelating agents indicated for the following uses:[1,2]

- **Cystinuria**.
- **Rheumatoid arthritis**, severe, active disease in patients who have failed to respond to an adequate trial of conventional therapy.
- **Wilson's disease** (hepatolenticular degeneration).

Product labeling for Cuprimine and Depen is identical, with the exception of the differences in dosage forms: Cuprimine is supplied as 250 mg capsules; Depen is supplied as 250 mg tablets.[1,2]

Guidelines

Penicillamine is discussed in the following guidelines:

- **Rheumatoid Arthritis:** Guidelines from American College of Rheumatology (2021) do not recommend the use of penicillamine for rheumatoid arthritis.[5]
- **Wilson's Disease:**
  The American Association for the Study of Liver Diseases (AASLD) provides guidelines for the diagnosis and management of Wilson's disease (2022).[3] Diagnosis of Wilson's disease is confirmed by conducting genetic testing confirming biallelic pathogenic *ATP7B* mutations or confirmation of at least two clinical features associated with Wilson's disease (Kayser-Fleischer rings, serum ceruloplasmin levels < 20 mg/dL, liver biopsy, 24-hour urinary copper > 40 mcg/24 hours). The AASLD recommends a chelating agent (penicillamine or trientine) for initial treatment in symptomatic patients. For the treatment of presymptomatic patients or those on maintenance therapy, chelating agents and zinc are both treatment options.

  The European Association for the Study of the Liver (EASL) also published a clinical practice guideline for the treatment of Wilson's disease (2012).[4] Like the AASLD, the EASL acknowledges that numerous studies have demonstrated the effectiveness of penicillamine. A chelating agent (penicillamine or trientine) is the recommended initial treatment of symptomatic patients and a chelating agent or zinc may be used for the treatment of presymptomatic patients or patients established on maintenance therapy. In patients with neurological disease established on maintenance therapy, either a chelating agent or zinc may be used; zinc may have a role as first-line therapy in these patients. If zinc is used, careful monitoring of transaminases is needed, with changing to chelators if these laboratory parameters are increasing.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of the penicillamine products. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with penicillamine products for Wilson's disease as well as the monitoring required for adverse events and long-term efficacy, approval for this condition requires penicillamine products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Cuprimine and penicillamine capsules is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Cystinuria. Approve for 1 year if the patient meets the following (A and B):

A) According to the prescriber, patient has tried increased fluid intake; restriction of sodium and protein; and urinary alkalinization; AND

B) Patient meets ONE of the following (i or ii):

i. Generic penicillamine capsules are requested; OR

ii. If brand Cuprimine is prescribed, patient has tried generic penicillamine capsules AND cannot take generic penicillamine capsules due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

2. Wilson's Disease. Approve for 1 year if the patient meets the following (A, B, C, and D):

A) Diagnosis of Wilson's disease is confirmed by ONE of the following (i or ii):

i. Genetic testing results confirming biallelic pathogenic *ATP7B* mutations (in either symptomatic or asymptomatic individuals); OR

ii. Confirmation of at least TWO of the following (TWO of a, b, c, or d):

a) Presence of Kayser-Fleischer rings;

b) Serum ceruloplasmin level < 20 mg/dL;

c) Liver biopsy findings consistent with Wilson's disease;

d) 24-hour urinary copper > 40 mcg/24 hours; AND

B) Patient meets ONE of the following (i, ii, iii, or iv):

i. Patient has tried Galzin (zinc acetate capsules); OR

ii. Patient has tried another zinc product (e.g., zinc sulfate, zinc gluconate, zinc acetate); OR

iii. According to the prescriber, patient has symptoms of Wilson's disease and zinc would not be an appropriate therapy; OR

iv. Patient has been started on therapy with a penicillamine product; AND

C) Patient meets ONE of the following (i or ii):

i. Generic penicillamine capsules are requested; OR

ii. If brand Cuprimine is prescribed, patient has tried generic penicillamine capsules AND cannot take generic penicillamine capsules due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction; AND

D) The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, or liver transplant physician.

II. Coverage of Depen and penicillamine tablets is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Cystinuria. Approve for 1 year if the patient meets the following (A and B):**
   - **A)** According to the prescriber, patient has tried increased fluid intake; restriction of sodium and protein; and urinary alkalinization; AND
   - **B)** Patient meets ONE of the following (i or ii):
     - **i. Generic penicillamine** tablets **are requested; OR**
     - **ii. If brand** Depen **is prescribed, patient has tried generic penicillamine tablets AND cannot take generic penicillamine tablets due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.**

2. **Wilson's Disease.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   - **A)** Diagnosis of Wilson's disease is confirmed by ONE of the following (i or ii):
     - **i.** Genetic testing results confirming biallelic pathogenic *ATP7B* mutations (in either symptomatic or asymptomatic individuals); OR
     - **ii.** Confirmation of at least two of the following (a, b, c, d):
       - **a)** Presence of Kayser-Fleischer rings;
       - **b)** Serum ceruloplasmin level < 20 mg/dL;
       - **c)** Liver biopsy findings consistent with Wilson's disease;
       - **d)** 24-hour urinary copper > 40 mcg/24 hours; AND
   - **B) Patient meets ONE of the following** (i, ii, iii, or iv):
     - **i.** Patient has tried Galzin (zinc acetate capsules); OR
     - **ii.** Patient has tried another zinc product (e.g., zinc sulfate, zinc gluconate, zinc acetate); OR
     - **iii.** According to the prescriber, patient has symptoms of Wilson's disease and zinc would not be an appropriate therapy; OR
     - **iv. Patient has been started on therapy with a penicillamine product; AND**
   - **C) P**atient meets ONE of the following (i or ii):
     - **i.** Generic penicillamine tablets are requested; OR
     - **ii.** If brand Depen is prescribed, patient has tried generic penicillamine tablets AND cannot take generic penicillamine tablets due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction; AND
   - **D)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, or liver transplant physician.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of penicillamine products is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

64. Cuprimine® capsules [prescribing information]. Bridgewater, NJ. Valeant; November 2019.
65. Depen® tablets [prescribing information]. Somerset, NJ. Meda; January 2019.
66. Schilsky ML, Roberts EA, et al. A multidisciplinary approach to the diagnosis and management of Wilson's disease: 2022 Practical Guidance on Wilson disease from the AASLD. *Hepatology*. 2023;77(4):1428-1455.
67. European Association for Study of the Liver (EASL) clinical practice guidelines: Wilson's disease. *J Hepatol*. 2012;56(3):671-85.
68. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2021 Jul;73(7):924-939.

PRIOR AUTHORIZATION POLICY

POLICY: Chelating Agents – Trientine Products Prior Authorization Policy
- Cuvrior™ (trientine tetrahydrochloride tablets – Orphalan)
- Syprine® (trientine hydrochloride capsules – Bausch, generic)

REVIEW DATE: 11/15/2023

OVERVIEW

Trientine products (capsules [Syprine, generics] and tablets [Cuvrior]) are chelating agents indicated for the treatment of **Wilson's disease** (hepatolenticular degeneration).[1,2]

Syprine (trientine hydrochloride capsules, generic) is indicated for the following use:[1]
- Treatment of patients with **Wilson's disease** who are intolerant of penicillamine.

Cuvrior (trientine tetrahydrochloride tablets) is indicated for the following use:[2]
- Treatment of adults with stable **Wilson's disease** who are de-coppered and tolerant to penicillamine.

Trientine is not indicated for use in patients with cystinuria, rheumatoid arthritis, or biliary cirrhosis.[1] Trientine products should be used when treatment with penicillamine is no longer possible because of intolerable or life-endangering side effects.[1] The content of trientine differs between products, thus they are not interchangeable on a mg per mg basis.[2]

Disease Overview

Wilson's disease is an autosomal recessive disorder in which alterations in cellular copper processing and impaired biliary excretion lead to copper accumulation.[3-5] Copper initially builds up in the liver and is eventually released into the bloodstream and deposited into other organs (e.g., brain, kidneys, and cornea) so it can cause a wide variety of symptoms. Lifelong pharmacologic therapy is the mainstay of treatment for Wilson's disease; without treatment, most patients will die from liver disease or progressive neurologic disease. Liver transplantation is reserved for severe or resistant cases. In patients with Wilson's disease, trientine acts as a general metal chelator and promotes urinary copper excretion as well as blocks dietary copper absorption.

Guidelines

The American Association for the Study of Liver Diseases (AASLD) provides guidelines for the diagnosis and management of Wilson's disease (2022).[4] Diagnosis of Wilson's disease is confirmed by conducting genetic testing confirming biallelic pathogenic *ATP7B* mutations or confirmation of at least two clinical features associated with Wilson's disease (Kayser-Fleischer rings, serum ceruloplasmin level < 20 mg/dL, liver biopsy, 24-hour urinary copper > 40 mcg/24 hours). The AASLD recommends a chelating agent (penicillamine or trientine) for initial treatment of symptomatic patients. For the treatment of presymptomatic patients or those on maintenance therapy, chelating agents and zinc are both treatment options.

The European Association for the Study of the Liver (EASL) also published a clinical practice guideline for the treatment of Wilson's disease (2012).[5] Like the AASLD, the EASL acknowledges that numerous studies have demonstrated the effectiveness of penicillamine. A chelating agent (penicillamine or trientine) is the recommended initial treatment of symptomatic patients, and a chelating agent or zinc may be used

for the treatment of presymptomatic patients or patients established on maintenance therapy. In patients with neurological disease established on maintenance therapy, either a chelating agent or zinc may be used; zinc may have a role as first-line therapy in these patients. If zinc is used, careful monitoring of transaminases is needed, with changing to chelators if these laboratory parameters are increasing.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of trientine products. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with trientine as well as the monitoring required for adverse events and long-term efficacy, approval requires trientine products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of trientine is recommended in those who meet the following criteria:

FDA-Approved Indication

3. Wilson's Disease. Approve for 1 year if the patient meets the following (A, B, and C):

E) Diagnosis of Wilson's disease is confirmed by ONE of the following (i or ii):

- **i.** Genetic testing results confirming biallelic pathogenic *ATP7B* mutations (in either symptomatic or asymptomatic individuals); OR
- **ii.** Confirmation of at least TWO of the following (TWO of a, b, c, or d):
  - **a)** Presence of Kayser-Fleischer rings;
  - **b)** Serum ceruloplasmin level < 20 mg/dL;
  - **c)** Liver biopsy findings consistent with Wilson's disease;
  - **d)** 24-hour urinary copper > 40 mcg/24 hours; AND

F) Patient meets ONE of the following (i, ii, iii, iv, v or vi):

- **i.** Patient has tried one penicillamine product and is intolerant to penicillamine therapy, according to the prescriber; OR
  Note: Examples of penicillamine products are Cuprimine (penicillamine capsules, generic), Depen (penicillamine tablets, generic).
- **ii.** According to the prescriber, patient has clinical features indicating the potential for intolerance to penicillamine therapy; OR
  Note: Specific clinical features include of any renal disease, congestive splenomegaly causing severe thrombocytopenia, autoimmune tendency.
- **iii.** Patient has a contraindication to penicillamine therapy, according to the prescriber; OR
- **iv.** Patient has neurologic manifestations of Wilson's disease; OR
- **v.** Patient is pregnant; OR
- **vi.** Patient has been started on therapy with trientine (Cuvrior or Syprine, generic).

G) The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, or liver transplant physician.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of trientine products is not recommended in the following situations:

54. Biliary Cirrhosis. Trientine is not indicated for the treatment of biliary cirrhosis.[1]

55. Cystinuria. Trientine is not recommended for use in patients with cystinuria.[1] Unlike penicillamine, trientine does not contain a sulfhydryl moiety and therefore it is not capable of binding cysteine.

56. Rheumatoid Arthritis. Trientine is not recommended for use in patients with rheumatoid arthritis.[1] Per the prescribing information, trientine was not found to be effective in improving any clinical or biochemical parameter after 12 weeks of treatment in patients with rheumatoid arthritis.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

69. Syprine® capsules [prescribing information]. Bridgewater, NJ: Bausch Health; September 2020.
70. Cuvrior™ tablets [prescribing information]. Chicago, IL: Orphalan SA; May 2022.
71. Weiss KH, Thurik F, Gotthardt DN, et al. Efficacy and safety of oral chelators in treatment of patients with Wilson Disease. *Clin Gastroenterol Hepatol*. 2013;11:1028-1035.
72. Schilsky ML, Roberts EA, et al. A multidisciplinary approach to the diagnosis and management of Wilson's disease: 2022 Practical Guidance on Wilson disease from the AASLD. *Hepatology*. 2023;77(4):1428-1455.
73. European Association for Study of the Liver (EASL) clinical practice guidelines: Wilson's disease. *J Hepatol*. 2012;56(3):671-85.

PRIOR AUTHORIZATION POLICY

POLICY: Chenodal Prior Authorization Policy
- Chenodal™ (chenodiol tablets – Travere)

REVIEW DATE: 08/23/2023

OVERVIEW

Chenodal, a naturally occurring bile acid, is indicated for patients with **radiolucent stones** in well-opacifying gallbladders, in whom selective surgery would be undertaken except for the presence of increased surgical risk due to systemic disease or age.[1]

The most widely used treatment for symptomatic gallstones is cholecystectomy.[2] Two naturally occurring bile acids are used in the treatment of gallstones: ursodeoxycholic acid (UrsoForte®, Urso-250®, [ursodiol tablets, generic], Actigall® [ursodiol capsules, generic]) and chenodeoxycholic acid/chenodiol (Chenodal).[3] These agents reduce biliary cholesterol; however, their exact mechanisms differ. Both Chenodal and ursodiol promote the gradual dissolution of radiolucent gallstones over a period of 6 months to 2 years.[2]

Other Uses with Supportive Evidence

Cerebrotendinous xanthomatosis (CTX) is a lipid storage disorder with various clinical manifestations including juvenile cataracts, tendon xanthomas, premature atherosclerosis, and progressive neurologic disturbance (e.g., ataxia, seizures, psychiatric disorders, and peripheral neuropathy).[4] Other conditions associated with CTX include osteoarthritis, skeletal fractures, pulmonary insufficiency, renal and hepatic calculi, and childhood chronic diarrhea. CTX is the result of a mutated enzyme (cytochrome P450 27-sterol hydroxylase) which is normally responsible for the conversion of cholesterol to cholic acid and chenodeoxycholic acid. In CTX, reduced synthesis of cholic and chenodeoxycholic acids results in failed feedback inhibition of cholesterol production, in turn leading to hallmark laboratory findings of the disorder: increased serum cholesterol concentrations and elevated urinary bile alcohols.[5] Replacement therapy with chenodiol inhibits abnormal bile acid synthesis and is most effective in reducing elevated plasma cholesterol concentrations and eliminating bile alcohols.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Chenodal. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Chenodal as well as the monitoring required for adverse events and long-term efficacy, approval requires Chenodal to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Chenodal is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. **Gallstones.** Approve for 1 year if the patient meets one of the following (A or B):
   A) Patient has tried an ursodiol product; OR
   B) Patient is currently receiving an ursodiol product.

Other Uses with Supportive Evidence

2. **Cerebrotendinous Xanthomatosis.** Approve for 1 year if Chenodal is prescribed by or in consultation with a metabolic specialist who treats patients with cerebrotendinous xanthomatosis or a specialist who focuses in the treatment of cerebrotendinous xanthomatosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Chenodal is not recommended in the following situations:

5. **Combination Therapy with Cholbam (cholic acid capsules)**. There are no efficacy data available to support use of combination therapy with Chenodal and Cholbam.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

126. Chenodal™ tablets [prescribing information]. San Diego, CA: Travere; May 2021.
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PRIOR AUTHORIZATION POLICY

POLICY: Cholbam Prior Authorization Policy
- Cholbam® (cholic acid capsules – Travere)

REVIEW DATE: 07/19/2023

OVERVIEW

Cholbam, a bile acid, is indicated for the following uses:[1]
- **Bile acid synthesis disorders due to single enzyme defects (SEDs)**.
- **Peroxisomal disorders (PDs), including Zellweger spectrum disorders**, as adjunctive treatment in patients who exhibit manifestations of liver disease, steatorrhea, or complications from decreased fat soluble vitamin absorption.

The effects of Cholbam on extrahepatic manifestations (e.g., neurologic symptoms) of bile acid synthesis disorders due to SEDs or PDs have not been established.[1] The prescribing information states that treatment with Cholbam should be discontinued if liver function does not improve within 3 months of the start of treatment or if complete biliary obstruction develops.

Bile Acid Synthesis Disorders

Bile acids are found in the liver and have several biological roles, including promotion of bile flow and intestinal absorption of fat and fat soluble vitamins.[2] The two primary bile acids are cholic acid and chenodeoxycholic acid (available as Chenodal® [chenodiol tablets]). Bile acids are formed from cholesterol; inadequate bile acid production leads to accumulation of cholesterol in the body, as well as other intermediary metabolites. This can result in damage to various organ systems. Severe cases may progress to cirrhosis and liver failure. Progressive neurologic disease may also occur, even in the absence of liver disease.

There are at least 17 known enzymes involved in bile acid synthesis. Primary bile acid synthesis disorders may be caused by a defect in the gene encoding any one of these enzymes. Enrollment criteria in the pivotal studies with Cholbam were based on abnormal urinary bile acids analysis by Fast Atom Bombardment ionization – mass spectrometry (FAB-MS).[1] However, gene sequencing is now available for many of the affected enzymes.

Peroxisomal Disorders (PDs)

PDs occur due to genetic mutations to genes that are essential to the proper formation of peroxisomes.[3] Among their many roles, peroxisomes are vital to the production of bile acids, as well as for neurologic function. Zellweger spectrum disorder is a type of PD and may be severe (Zellweger syndrome) or intermediate/milder (previously called neonatal adrenoleukodystrophy, infantile Refsum disease, or Heimler syndrome).[4] Enrollment criteria in the pivotal trials were based on abnormal urinary bile acids analysis by FAB-MS and a neurologic exam.[1] However, molecular genetic testing is now available.[4]

GUIDELINES

A joint guideline by the North American and European Societies for Pediatric Gastroenterology, Hepatology, and Nutrition is available (2017).[5] The guideline, which briefly addresses evaluation of cholestatic jaundice in infants, provides recommendations for diagnosis of bile acid synthesis disorders. While it is possible to perform rapid diagnosis of potential inborn errors in bile acid synthesis from urinary

bile acid analysis, FAB-MS of urine is recommended. The guideline also notes that molecular techniques identify the specific mutations in genes encoding enzymes responsible for bile acid synthesis.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cholbam. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cholbam as well as the monitoring required for adverse events and long-term efficacy, approval requires Cholbam to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cholbam is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Bile Acid Synthesis Disorders Due to Single Enzyme Defects (SEDs).** Approve for the duration noted if the patient meets one of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets both of the following (i and ii):
     - **i.** Patient has at least one of the following (a or b):
       - An abnormal urinary bile acid as confirmed by Fast Atom Bombardment ionization – Mass Spectrometry (FAB-MS) analysis; OR
       - Molecular genetic testing consistent with the diagnosis; AND
     - **ii.** The medication is prescribed by or in consultation with a hepatologist, metabolic specialist, or gastroenterologist.
   - **B)** Patient is Currently Receiving Cholbam. Approve for 1 year if the patient meets the following (i, ii, and iii):
     - **i.** Patient has responded to initial Cholbam therapy with an improvement in liver function tests (e.g., aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin levels); AND
     - **ii.** Patient does not have complete biliary obstruction; AND
     - **iii.** The medication is prescribed by or in consultation with a hepatologist, metabolic specialist, or gastroenterologist.

2. **Bile Acid Synthesis Disorders Due to Peroxisomal Disorders (PDs), Including Zellweger Spectrum Disorders.** Approve for the duration noted if the patient meets one of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets the following (i, ii, and iii):
     - **i.** Patient has peroxisomal disorders with at least one of the following (a or b):
       - An abnormal urinary bile acid analysis by Fast Atom Bombardment ionization – Mass Spectrometry (FAB-MS); OR
       - Molecular genetic testing consistent with the diagnosis; AND
     - **ii.** Patient has liver disease, steatorrhea, or complications from decreased fat soluble vitamin absorption (e.g., rickets); AND
     - **iii.** The medication is prescribed by or in consultation with a hepatologist, metabolic specialist, or gastroenterologist.

B) Patient is Currently Receiving Cholbam. Approve for 1 year if the patient meets the following (i, ii, and iii):

i. Patient has responded to initial Cholbam therapy according to the prescriber; AND
- Note: Examples of a response to initial Cholbam therapy include improvements in liver enzymes or improvement in steatorrhea.

ii. Patient does not have complete biliary obstruction; AND

iii. The medication is prescribed by or in consultation with a hepatologist, metabolic specialist, or gastroenterologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cholbam is not recommended in the following situations:

57. Concomitant Use with Chenodal. There are no efficacy data available to support concomitant use of Cholbam and Chenodal.

58. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Cinacalcet Prior Authorization Policy
- Sensipar® (cinacalcet tablets – Amgen, generic)

REVIEW DATE: 03/01/2023

Overview

Cinacalcet, a calcium-sensing receptor agonist (calcimimetic), is indicated for the following uses:[1]

- **Hypercalcemia parathyroid carcinoma** in adults.
- **Hypercalcemia with primary hyperparathyroidism** in adults for whom parathyroidectomy would be indicated on the basis of serum calcium levels, but who are unable to undergo parathyroidectomy.
- **Secondary hyperparathyroidism** with chronic kidney disease (CKD) in adults on dialysis.

Limitation of use: Cinacalcet is not indicated for use in patients with CKD who are not on dialysis due to increased risk of hypocalcemia.

Disease Overview

Secondary hyperparathyroidism is a frequent complication of CKD caused by a reduction in circulating calcitriol levels and disturbances in calcium and phosphorous metabolism.[2] This leads to increases in the parathyroid hormone (PTH) levels, which then leads to osteoclastic activity resulting in bone resorption and marrow fibrosis.

Parathyroid carcinoma, a rare malignant cancer, is an uncommon cause of primary hyperparathyroidism.[3] The condition is associated with higher serum calcium and PTH levels than primary hyperparathyroidism due to benign adenoma. The primary cause of morbidity in patients with parathyroid carcinoma is due to complications of hypercalcemia (e.g., cardiac arrhythmias, renal failure). Surgical resection of the malignancy may relieve symptoms and reduce serum calcium levels. Medical therapy with cinacalcet and intravenous bisphosphonates are useful adjunct therapies to control hypercalcemia.

Guidelines

The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines (2009; updated 2017) for the treatment of CKD-mineral bone disorder (CKD-MBD) consider calcimimetics (cinacalcet), calcitriol, or vitamin D analogs (or a combination of these agents) as reasonable first line options for patients with CKD stage 5D who require PTH-lowering therapy.[4,5] If intact parathyroid hormone (iPTH) levels fall below two times the upper limit of normal for the assay, these products should be reduced or discontinued

Other Uses with Supportive Evidence

The KDIGO clinical practice guidelines (2017) for the treatment of CKD-MBD note that although cinacalcet is not approved for the treatment of hyperparathyroidism in kidney transplant recipients, it is used in these patients, especially those with significant hypercalcemia.[4,5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of cinacalcet. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with cinacalcet as well as the monitoring required for adverse events and long-term efficacy, approval requires cinacalcet to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: When available, the ICD-9/ICD-10 codes for Malignant Neoplasm of Parathyroid Gland (ICD-9: 194.1* and ICD-10: C75.0*) AND "oncologist or endocrinologist" will be used as part of automation to allow approval of the requested medication.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of cinacalcet is recommended in those who meet one of the following criteria:

FDA-Approved Indications

3. **Hypercalcemia due to Parathyroid Carcinoma.** Approve for 1 year if cinacalcet is prescribed by or in consultation with an oncologist or endocrinologist.

4. **Hypercalcemia in a Patient with Primary Hyperparathyroidism.** Approve for 1 year if the patient meets both of the following criteria (A and B):
   - **A)** Patient has failed or is unable to undergo a parathyroidectomy due to a contraindication; AND
   - **B)** The medication is prescribed by or in consultation with a nephrologist or endocrinologist.

5. **Secondary Hyperparathyroidism.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** Patient has chronic kidney disease; AND
   - **B)** Patient is on dialysis; AND
   - **C)** The baseline (prior to starting cinacalcet therapy) intact parathyroid hormone (iPTH) level is at least two times the upper limit of normal as defined by the laboratory reference value measured on two separate occasions; AND
   - **D)** The medication is prescribed by or in consultation with a nephrologist or endocrinologist.

Other Uses with Supportive Evidence

6. **Hyperparathyroidism in a Post-Renal Transplant Patient.** Approve for 1 year if the patient meets both of the following conditions (A and B):
   - **A)** The baseline (prior to starting cinacalcet therapy) calcium and intact parathyroid hormone (iPTH) levels are above the normal range, as defined by the laboratory reference values; AND
   - **B)** The medication is prescribed by or in consultation with a transplant physician, nephrologist, or endocrinologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of cinacalcet is not recommended in the following situations:

59. **Patient with Primary Hyperparathyroidism Eligible for Parathyroidectomy.** Parathyroidectomy is the primary treatment for primary hyperparathyroidism.

60. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Colony Stimulating Factors – Filgrastim Products Prior Authorization Policy
- Neupogen® (filgrastim intravenous or subcutaneous injection – Amgen)
- Nivestym™ (filgrastim-aafi intravenous or subcutaneous injection – Hospira/Pfizer)
- Releuko® (filgrastim-ayow intravenous or subcutaneous injection – Amneal)
- Zarxio® (filgrastim-sndz intravenous or subcutaneous injection – Sandoz)

REVIEW DATE: 09/20/2023

OVERVIEW

Filgrastim, a leukocyte growth factor, is indicated for the following uses:[1-4]

- **Decrease the incidence of infection as manifested by febrile neutropenia**, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.
- **Mobilization of hematopoietic progenitor cells,** into the peripheral blood for collection by leukapheresis.
- **Reduce the time to neutrophil recovery and the duration of fever,** following induction or consolidation chemotherapy treatment of adults with acute myeloid leukemia (AML).
- **Reduce the duration of neutropenia and neutropenia-related clinical sequelae (e.g., febrile neutropenia),** in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation.
- **Reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers),** in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

Nivestym, Releuko, and Zarxio are biosimilars to Neupogen.[2-4] Releuko indication labeling does not include mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.[4] Neupogen is additionally indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) addresses the use of filgrastim products in several guidelines.

- **Acute Lymphoblastic Leukemia (ALL):** Guidelines (version 2.2023 – July 28, 2023) recommend granulocyte colony stimulating factors (CSFs) as supportive care for myelosuppressive blocks of therapy or as directed by treatment protocol.[5]
- **Hematopoietic Cell Transplantation:** Guidelines (version 1.2023 – March 31, 2023) recommend filgrastim for hematopoietic cell mobilization for allogeneic or autologous donors as a single agent or in combination with other treatments.[6]
- **Hematopoietic Growth Factors:** Guidelines (version 2.2023 – March 6, 2023) recommend filgrastim, along with other CSFs, for prophylactic use if the patient is receiving anti-cancer medications that are associated with a high (> 20%) incidence of severe neutropenia with fever.[7] Consider CSF therapy for patients with an intermediate (10% to 20%) probability of developing febrile neutropenia based on risk factors. The NCCN guidelines also recommend therapy with CSFs in other scenarios in those given myelosuppressive chemotherapy. Filgrastim products are also recommended for mobilization and following hematopoietic cell transplant.

- **Management of Immunotherapy-Related Toxicities:** Guidelines (version 2.2023 – May 9, 2023) recommend granulocyte CSFs as supportive care for neutropenic patients with Grade 1 cytokine release syndrome resulting from chimeric antigen receptor T-cell therapy.[8]
- **Myelodysplastic Syndromes (MDS):** Guidelines (version 1.2023 – September 12, 2022) consider filgrastim for use in certain patients (e.g., neutropenic patients with recurrent or resistant infections, combination use with epoetin alfa or Aranesp® [darbepoetin alfa injection] in patients with anemia).[9]

The American Society of Clinical Oncology clinical practice guidelines for the use of white blood cell growth factors (2015) recommend CSFs to reduce the risk of febrile neutropenia in patients receiving cancer chemotherapy.[10] CSFs may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected. The guidelines state CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum.

Other Uses with Supportive Evidence

Neutropenia occurs in patients with human immunodeficiency virus (HIV) and may be caused by medications or due to the disease process. Studies have demonstrated positive outcomes with the use of filgrastim for the treatment of neutropenia in this patient population.[11-14]

Filgrastim has been used for agranulocytosis caused by non-cytotoxic medications, primarily described in case series, case reports and literature reviews.[15-21]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of filgrastim products. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with filgrastim products as well as the monitoring required for adverse events and long-term efficacy, approval for some conditions requires filgrastim products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of filgrastim products is recommended in those who meet one of the following:

FDA-Approved Indications

1. **Acute Myeloid Leukemia (AML) in a Patient Receiving Chemotherapy.** Approve for 6 months if prescribed by or in consultation with an oncologist or hematologist.

2. **Bone Marrow Transplant in a Patient with Cancer Who Received Chemotherapy.** Approve for 1 month if prescribed by or in consultation with a hematologist, an oncologist, or a physician who specializes in transplantation.

3. **Cancer in a Patient Receiving Myelosuppressive Chemotherapy.** Approve for 6 months if the patient meets the following (A and B):
   A) Patient meets ONE of the following (i, ii, iii, or iv):

i. Patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk is at least 20% based on the chemotherapy regimen); OR

ii. Patient meets both of the following (a and b):
   1. Patient is receiving myelosuppressive anti-cancer medications that are associated with a risk of febrile neutropenia, but the risk is less than 20% based on the chemotherapy regimen; AND
   2. Patient has at least one risk factor for febrile neutropenia according to the prescriber; OR
      Note: Examples of risk factors include age ≥ 65 years; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver and/or renal dysfunction; poor performance status; or human immunodeficiency virus (HIV) infection.

iii. Patient meets both of the following (a and b):
   1. Patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor; AND
      Note: Examples of colony stimulating factors include filgrastim products, pegfilgrastim products, and sargramostim products (e.g., Leukine).
   2. A reduced dose or frequency of chemotherapy may compromise treatment outcome; OR

iv. Patient who has received chemotherapy has febrile neutropenia and has at least one risk factor for poor clinical outcomes or for developing infection-associated complications according to the prescriber; AND
   Note: Examples of risk factors include sepsis syndrome; age > 65 years; severe neutropenia (absolute neutrophil count [ANC] < 100 cells/mm^3); neutropenia expected to be > 10 days in duration; invasive fungal infection; or other clinically documented infections.

B) The medication is prescribed by or in consultation with an oncologist or hematologist.

4. **Peripheral Blood Progenitor Cell Collection and Therapy.** Approve for 1 month if prescribed by or in consultation with an oncologist, a hematologist, or a physician who specializes in transplantation.

5. **Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome).** Approve for 1 month if prescribed by or in consultation with a physician who has expertise in treating acute radiation syndrome.

6. **Severe Chronic Neutropenia (e.g., Congenital Neutropenia, Cyclic Neutropenia, Idiopathic Neutropenia).** Approve for 6 months if prescribed by or in consultation with a hematologist.

Other Uses with Supportive Evidence

7. **Acute Lymphoblastic Leukemia (ALL).** Approve for 1 month if prescribed by or in consultation with an oncologist or a hematologist.

8. **Cytokine Release Syndrome associated with Chimeric Antigen Receptor (CAR) T-Cell Therapy.** Approve for 1 month if prescribed for a patient who has neutropenia.
   Note: Examples of CAR T-cell therapy include Kymriah (tisagenlecleucel intravenous infusion) and Yescarta (axicabtagene ciloleucel intravenous infusion).

9. **Drug-Induced (Non-Chemotherapy) Agranulocytosis or Neutropenia.** Approve for 1 month.

10. **Myelodysplastic Syndromes (MDS).** Approve for 3 months if prescribed by or in consultation with an oncologist or hematologist.

11. Neutropenia Associated with Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome (AIDS). Approve for 4 months if the agent is prescribed by or in consultation with a physician who specializes in infectious diseases, a hematologist, or a physician who specializes in the management of HIV/AIDS.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of filgrastim products is not recommended in the following situations:

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Colony Stimulating Factors – Granix Prior Authorization Policy
- Granix® (tbo-filgrastim subcutaneous injection – Teva)

REVIEW DATE: 09/20/2023

OVERVIEW

Granix, a leukocyte growth factor, is indicated to reduce the duration of severe neutropenia in adults and pediatric patients ≥ 1 month of age with non-myeloid malignancies receiving myelosuppressive anti-cancer medications associated with a clinically significant incidence of febrile neutropenia.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) addresses the use of Granix in guidelines.

- **Hematopoietic Cell Transplantation:** Guidelines (version 1.2023 – March 31, 2023) recommend filgrastim for hematopoietic cell mobilization for allogeneic or autologous donors as a single agent or in combination with other treatments.[4] NCCN states Granix is an appropriate substitute for filgrastim.
- **Hematopoietic Growth Factors:** Guidelines (version 2.2023 – March 6, 2023) recommend Granix, along with other granulocyte colony stimulating factors (CSFs), for prophylactic use if the patient is receiving anti-cancer medications that are associated with a high (> 20%) incidence of severe neutropenia with fever.[2] Consider CSF therapy for patients with an intermediate (10% to 20%) probability of developing febrile neutropenia based on risk factors. The NCCN guidelines also recommend therapy with CSFs in other scenarios in those given myelosuppressive chemotherapy. Granix is also recommended for mobilization and following hematopoietic cell transplant.
- **Myelodysplastic Syndromes (MDS):** Guidelines (version 1.2023 – September 12, 2022) recommend Granix for use in certain patients with MDS (e.g., neutropenic patients with recurrent or resistant infections, combination use with epoetin alfa or Aranesp® [darbepoetin alfa injection] in patients with anemia).[3]

The American Society of Clinical Oncology clinical practice guidelines for the use of white blood cell growth factors (2015) recommends CSFs to reduce the risk of febrile neutropenia in patients receiving cancer chemotherapy.[5] CSFs may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected. The guidelines state CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Granix. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Granix as well as the monitoring required for adverse events and long-term efficacy, approval requires Granix to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Granix is recommended in those who meet one of the following criteria:

FDA-Approved Indication

12. Cancer in a Patient Receiving Myelosuppressive Chemotherapy. Approve for 6 months if the patient meets the following (A and B):

B) Patient meets ONE of the following (i, ii, iii, or iv):

i. Patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk is at least 20% based on the chemotherapy regimen); OR

ii. Patient meets both of the following (a and b):

a. Patient is receiving myelosuppressive anti-cancer medications that are associated with a risk of febrile neutropenia, but the risk is less than 20% based on the chemotherapy regimen; AND

b. Patient has at least one risk factor for febrile neutropenia according to the prescriber; OR
Note: Examples of risk factors include age ≥ 65 years; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver and/or renal dysfunction; poor performance status; or human immunodeficiency virus (HIV) infection.

iii. Patient meets both of the following (a and b):

a. Patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor; AND
Note: Examples of colony stimulating factors include filgrastim products, pegfilgrastim products, and sargramostim products (e.g., Leukine).

b. A reduced dose or frequency of chemotherapy may compromise treatment outcome; OR

iv. Patient who has received chemotherapy has febrile neutropenia and has at least one risk factor for poor clinical outcomes or for developing infection-associated complications according to the prescriber; AND
Note: Examples of risk factors include sepsis syndrome; age > 65 years; severe neutropenia (absolute neutrophil count [ANC] < 100 cells/mm^3); neutropenia expected to be > 10 days in duration; invasive fungal infection; or other clinically documented infections.

B) The medication is prescribed by or in consultation with an oncologist or hematologist.

Other Uses with Supportive Evidence

13. Myelodysplastic Syndromes (MDS). Approve for 3 months if prescribed by or in consultation with an oncologist or hematologist.

14. Peripheral Blood Progenitor Cell Collection and Therapy. Approve for 1 month if prescribed by or in consultation with an oncologist, a hematologist, or a physician who specializes in transplantation.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Granix is not recommended in the following situations:

8. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

22. Granix® subcutaneous injection [prescribing information]. North Wales, PA: Teva; April 2020.
23. The NCCN Hematopoietic Growth Factors Clinical Practice Guidelines in Oncology (version 2.2023 – March 6, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 7, 2023.
24. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 1.2023 – September 12, 2022). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 7, 2023.
25. The NCCN Hematopoietic Cell Transplantation Clinical Practice Guidelines in Oncology (version 1.2023 – March 31, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 7, 2023.
26. Smith TJ, Bohlke K, Lyman GH, Carson KR, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2015;33(28):3199-3212.

PRIOR AUTHORIZATION POLICY

POLICY: Colony Stimulating Factors – Leukine Prior Authorization Policy
- Leukine® (sargramostim intravenous or subcutaneous injection – Partner Therapeutics)

REVIEW DATE: 09/20/2023

OVERVIEW

Leukine, a recombinant human granulocyte macrophage colony stimulating factor (GM-CSF), is indicated for the following uses:[1]

- **Acute exposure to myelosuppressive doses of radiation,** to increase survival in adult and pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).
- **Acute myeloid leukemia (AML) following induction chemotherapy**, to shorten the time to neutrophil recovery and to reduce the incidence of severe, life-threatening, or fatal infections in patients ≥ 55 years of age.
- **Allogeneic bone marrow transplantation,** for acceleration of myeloid reconstitution in adult and pediatric patients ≥ 2 years of age undergoing allogeneic bone marrow transplantation from human leukocyte antigen (HLA)-matched related donors.
- **Allogeneic or autologous bone marrow transplantation: treatment of delayed neutrophil recovery or graft failure,** treatment of patients ≥ 2 years of age who have undergone allogeneic or autologous bone marrow transplantation in whom neutrophil recovery is delayed or failed.
- **Autologous peripheral blood progenitor cell mobilization and collection,** in adult patients with cancer undergoing autologous hematopoietic stem cell transplantation for the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis.
- **Autologous peripheral blood progenitor cell (PBPC) and bone marrow transplantation,** for acceleration of myeloid reconstitution after autologous PBPC or bone marrow transplantation in adult and pediatric patients ≥ 2 years of age with non-Hodgkin's lymphoma, acute lymphoblastic leukemia, and Hodgkin's lymphoma.

Other Uses with Supportive Evidence

Unituxin® (dinutuximab intravenous infusion) is indicated for use in combination with GM-CSF, interleukin-2, and 13-cis-retinoic acid for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to first-line multiagent, multimodality therapy.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Leukine. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Leukine as well as the monitoring required for adverse events and long-term efficacy, approval requires Leukine to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Leukine is recommended in those who meet one of the following criteria:

FDA-Approved Indications

33. Acute Myeloid Leukemia. Approve for 6 months if the medication is prescribed by or in consultation with an oncologist or a hematologist.

34. Bone Marrow Transplant. Approve for 1 month if the medication is prescribed by or in consultation with a hematologist, an oncologist, or a physician who specializes in transplantation.

35. Peripheral Blood Progenitor Cell Collection and Therapy. Approve for up to 14 days if the medication is prescribed by or in consultation with an oncologist, a hematologist, or a physician that specializes in transplantation.

36. Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome). Approve for 1 month if the medication is prescribed by or in consultation with a physician with expertise in treating acute radiation syndrome.

Other Uses with Supportive Evidence

37. Neuroblastoma. Approve for 6 months if the patient meets the following (A, B, and C):
- **A)** Patient is < 18 years of age; AND
- **B)** Patient is receiving Leukine in a regimen with Unituxin (dinutuximab intravenous infusion); AND
- **C)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Leukine is not recommended in the following situations:

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

131. Leukine® intravenous or subcutaneous injection [prescribing information]. Lexington, MA: Partner Therapeutics; August 2023.
132. Unituxin™ intravenous infusion [prescribing information]. Silver Springs, MD: United Therapeutic; March 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Colony Stimulating Factors – Pegfilgrastim Products Prior Authorization Policy
- **Neulasta**® (pegfilgrastim subcutaneous injection – Amgen)
- Fulphila™ (pegfilgrastim-jmdb subcutaneous injection – Mylan)
- Fylnetra® (pegfilgrastim-pbbk subcutaneous injection – Kashiv)
- Nyvepria™ (pegfilgrastim-apgf subcutaneous injection – Pfizer)
- Stimufend® (pegfilgrastim-fpgk subcutaneous injection – Fresenius Kabi)
- Udenyca® (pegfilgrastim-cbqv subcutaneous injection – Coherus)
- Ziextenzo™ (pegfilgrastim-bmez subcutaneous injection – Sandoz)

REVIEW DATE: 09/20/2023

OVERVIEW

Pegfilgrastim, a leukocyte growth factor, is indicated to **decrease the incidence of infection as manifested by febrile neutropenia**, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.[1-5,11,12]

Fulphila, Fylnetra, Nyvepria, Stimufend, Udenyca, and Ziextenzo are biosimilars to Neulasta.[1-5,11,12] Neulasta is additionally indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) addresses the use of pegfilgrastim products in several guidelines.

- **Hematopoietic Cell Transplantation:** Guidelines (version 1.2023 – March 31, 2023) recommend pegfilgrastim for hematopoietic cell mobilization for autologous donors in combination with other treatments.[6] Currently, there is no recommendation for use of pegfilgrastim for stem cell mobilization in allogeneic donors.
- **Hematopoietic Growth Factors:** Guidelines (version 2.2023 – March 6, 2023) recommend pegfilgrastim, along with other colony stimulating factors (CSFs), for prophylactic use if the patient is receiving anti-cancer medications that are associated with a high (> 20%) incidence of severe neutropenia with fever.[7] Consider CSF therapy for patients with an intermediate (10% to 20%) probability of developing febrile neutropenia based on risk factors. The NCCN guidelines also recommend therapy with CSFs in other scenarios in those given myelosuppressive chemotherapy.

The American Society of Clinical Oncology clinical practice guidelines for the use of white blood cell growth factors (2015) recommends CSFs to reduce the risk of febrile neutropenia in patients receiving cancer chemotherapy.[8] CSFs may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected. The guidelines state CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of pegfilgrastim. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with pegfilgrastim as well as the monitoring required for adverse events and long-term efficacy, approval

requires pegfilgrastim to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of pegfilgrastim products is recommended in those who meet one of the following criteria:

FDA-Approved Indications

15. **Cancer in a Patient Receiving Myelosuppressive Chemotherapy**. Approve for 6 months if the patient meets the following (A and B):
    - **A)** Patient meets ONE of the following (i, ii, or iii):
        - **i.** Patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk is at least 20% based on the chemotherapy regimen); OR
        - **ii.** Patient meets both of the following (a and b):
            - **a)** Patient is receiving myelosuppressive anti-cancer medications that are associated with a risk of febrile neutropenia, but the risk is less than 20% based on the chemotherapy regimen; AND
            - **b)** Patient has at least one risk factor for febrile neutropenia according to the prescriber; OR
              Note: Examples of risk factors include age ≥ 65 years; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver and/or renal dysfunction; poor performance status; or human immunodeficiency virus (HIV) infection.
        - **iii.** Patient meets both of the following (a and b):
            - **a)** Patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor; AND
              Note: Examples of colony-stimulating factors include filgrastim products, pegfilgrastim products, and sargramostim products (e.g., Leukine).
            - **b)** A reduced dose or frequency of chemotherapy may compromise treatment outcome; AND
        - **B)** The medication is prescribed by or in consultation with an oncologist or hematologist.

2. **Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome).** Approve for 1 month if the agent is prescribed by or in consultation with a physician who has expertise in treating acute radiation syndrome.

Other Uses with Supportive Evidence

3. **Peripheral Blood Progenitor Cell Transplantation (PBPC) in Patients with Cancer.** Approve one dose if prescribed by or in consultation with an oncologist, a hematologist, or a physician who specializes in transplantation.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of pegfilgrastim products is not recommended in the following situations:

10. **Myelodysplastic Syndrome (MDS).** Only limited data report use of pegfilgrastim for patients with MDS.[9] Guidelines from the NCCN for MDS (version 1.2023 – September 12, 2022) do not mention use of pegfilgrastim in this patient population.[10]

8.

11. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

27. Neulasta® subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; March 2021.
28. Fulphila® subcutaneous injection [prescribing information]. Rockford, IL: Mylan; October 2021.
29. Udenyca® subcutaneous injection [prescribing information]. Redwood City, CA: Coherus BioSciences; March 2023.
30. Ziextenzo™ subcutaneous injection [prescribing information]. Princeton, NJ: Sandoz; March 2021.
31. Nyvepria™ subcutaneous injection [prescribing information]. New York, NY: Pfizer; June 2023.
32. The NCCN Hematopoietic Cell Transplantation Clinical Practice Guidelines in Oncology (version 1.2023 – March 31, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 7, 2023.
33. The NCCN Hematopoietic Growth Factors Clinical Practice Guidelines in Oncology (version 2.2023 – March 6, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 7, 2023.
34. Smith TJ, Bohlke K, Lyman GH, Carson KR, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2015;33(28):3199-3212.
35. Jakob A, Hirsch FW, Engelhardt M. Successful treatment of a patient with myelodysplastic syndrome (RAEB) with darbepoetin alfa in combination with pegfilgrastim. *Ann Hematol*. 2005;84(10):694-695.
36. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 1.2023 – September 12, 2022). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 7, 2023.
37. Fylnetra® subcutaneous injection [prescribing information]. Piscataway, NJ: Kashiv; May 2022.
38. Stimufend® subcutaneous injection [prescribing information]. Lake Zurich, IL: Fresenius Kabi; September 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Colony Stimulating Factors – Rolvedon Prior Authorization Policy
- Rolvedon™ (eflapegrastim-xnst subcutaneous injection – Spectrum)

REVIEW DATE: 09/20/2023; selected revision 12/20/2023

OVERVIEW

Rolvedon, a leukocyte growth factor, is indicated to **decrease the incidence of infection, as manifested by febrile neutropenia**, in adults with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.[1]

Limitation of use: Rolvedon is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.[1]

Safety and effectiveness in pediatric patients have not been established.[1]

Guidelines

According to the National Comprehensive Cancer Network (NCCN) guidelines for **hematopoietic growth factors** (version 2.2024 – December 12, 2023), evaluation of risk for febrile neutropenia following chemotherapy in adults with solid tumors and non-myeloid malignancies should occur prior to the first chemotherapy cycle.[2] For a patient at high risk (> 20% risk), granulocyte colony-stimulating factor (G-CSF) is recommended (category 1). For a patient at intermediate risk (10% to 20% risk), consider G-CSF if the patient has at least one of the following risk factors: including prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver dysfunction; renal dysfunction; and age > 65 years receiving full chemotherapy dose intensity (category 2A). Evaluation prior to second and subsequent chemotherapy cycles should also be completed and patients who experienced febrile neutropenia or a dose-limiting neutropenic event without prior use of G-CSFs in which a reduction in dose or frequency is not appropriate, the use of G-CSFs should be considered (category 2A). Recommended G-CSFs include filgrastim (category 1), Granix® (tbo-filgrastim subcutaneous injection) [category 1], pegfilgrastim (category 1), Rolvedon (category 2A), and Ryzneuta® (efbemalenograstim alfa-vuxw subcutaneous injection) [category 2A]. It is noted that the long-acting CSFs, pegfilgrastim, Rolvedon, and Ryzneuta® (efbemalenograstim alfa-vuxw subcutaneous injection), have only been studied for prophylactic use, not for treatment of febrile neutropenia. For treatment of a patient with radiation-induced myelosuppression following a radiologic/nuclear incident, therapeutic use of filgrastim, pegfilgrastim, Granix® (tbo-filgrastim subcutaneous injection), Leukine® (sargramostim subcutaneous injection), Rolvedon, or Ryzneuta® (efbemalenograstim alfa-vuxw subcutaneous injection) may be used (category 2A). Of note, throughout the recommendations, it is acknowledged that an FDA-approved biosimilar is an appropriate substitute for filgrastim or pegfilgrastim.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Rolvedon. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Rolvedon as well as the monitoring required for adverse events and long-term efficacy, approval requires Rolvedon to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rolvedon is recommended in those who meet the following criteria:

FDA-Approved Indication

16. Cancer in a Patient Receiving Myelosuppressive Chemotherapy. Approve for 6 months if the patient meets the following (A, B, and C):

B) Patient is ≥ 18 years of age; AND

C) Patient meets ONE of the following (i, ii, or iii):

v. Patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk is at least 20% based on the chemotherapy regimen); OR

vi. Patient meets both of the following (a and b):

1. Patient is receiving myelosuppressive anti-cancer medications that are associated with a risk of febrile neutropenia, but the risk is less than 20% based on the chemotherapy regimen; AND
2. Patient has at least one risk factor for febrile neutropenia according to the prescriber; OR
   Note: Examples of risk factors include age ≥ 65 years; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver and/or renal dysfunction; poor performance status; or human immunodeficiency virus (HIV) infection.

vii. Patient meets both of the following (a and b):

1. Patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor; AND
   Note: Examples of colony stimulating factors include filgrastim products, pegfilgrastim products, and Ryzneuta.
2. A reduced dose or frequency of chemotherapy may compromise treatment outcome; AND

D) The medication is prescribed by or in consultation with an oncologist or hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rolvedon is not recommended in the following situations:

12. Peripheral Blood Progenitor Cell Collection and Therapy. As a limitation of use in the Rolvedon prescribing information, it is noted that Rolvedon is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.[1]

13. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

39. Rolvedon™ subcutaneous injection [prescribing information]. Irvine, CA: Spectrum; June 2023.
40. The NCCN Hematopoietic Growth Factors Clinical Practice Guidelines in Oncology (version 2.2024 – December 12, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 12, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Colony Stimulating Factors – Ryzneuta Prior Authorization Policy
- Ryzneuta® (efbemalenograstim alfa-vuxw subcutaneous injection – Evive)

REVIEW DATE: 12/20/2023

OVERVIEW

Ryzneuta, a leukocyte growth factor, is indicated to **decrease the incidence of infection, as manifested by febrile neutropenia**, in adults with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.[1]

Limitation of use: Ryzneuta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.[1]

Safety and effectiveness in pediatric patients have not been established.[1]

Guidelines

According to the National Comprehensive Cancer Network (NCCN) guidelines for **hematopoietic growth factors** (version 2.2024 – December 12, 2023), evaluation of risk for febrile neutropenia following chemotherapy in adults with solid tumors and non-myeloid malignancies should occur prior to the first chemotherapy cycle.[2] For a patient at high risk (> 20% risk), granulocyte colony-stimulating factor (G-CSF) is recommended (category 1). For a patient at intermediate risk (10% to 20% risk), consider G-CSF if the patient has at least one of the following risk factors: including prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver dysfunction; renal dysfunction; and age > 65 years receiving full chemotherapy dose intensity (category 2A). Evaluation prior to second and subsequent chemotherapy cycles should also be completed and patients who experienced febrile neutropenia or a dose-limiting neutropenic event without prior use of G-CSFs in which a reduction in dose or frequency is not appropriate, the use of G-CSFs should be considered (category 2A). Recommended G-CSFs include filgrastim (category 1), Granix® (tbo-filgrastim subcutaneous injection) [category 1], pegfilgrastim (category 1), Rolvedon™ (eflapegrastim-xnst subcutaneous injection) [category 2A], and Ryzneuta (category 2A). It is noted that the long-acting G-CSFs, pegfilgrastim, Rolvedon, and Ryzneuta, have only been studied for prophylactic use, not for treatment of febrile neutropenia. For treatment of a patient with radiation-induced myelosuppression following a radiologic/nuclear incident, therapeutic use of filgrastim, pegfilgrastim, Granix® (tbo-filgrastim subcutaneous injection), Leukine® (sargramostim subcutaneous injection), Rolvedon™ (eflapegrastim-xnst subcutaneous injection), or Ryzneuta may be used (category 2A). Of note, throughout the recommendations, it is acknowledged that an FDA-approved biosimilar is an appropriate substitute for filgrastim or pegfilgrastim.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ryzneuta. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ryzneuta as well as the monitoring required for adverse events and long-term efficacy, approval requires Ryzneuta to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ryzneuta is recommended in those who meet the following criteria:

FDA-Approved Indication

17. Cancer in a Patient Receiving Myelosuppressive Chemotherapy. Approve for 6 months if the patient meets the following (A, B, and C):

E) Patient is ≥ 18 years of age; AND

F) Patient meets ONE of the following (i, ii, or iii):

viii. Patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk is at least 20% based on the chemotherapy regimen); OR

ix. Patient meets both of the following (a and b):

1. Patient is receiving myelosuppressive anti-cancer medications that are associated with a risk of febrile neutropenia, but the risk is less than 20% based on the chemotherapy regimen; AND
2. Patient has at least ONE risk factor for febrile neutropenia according to the prescriber; OR
   Note: Examples of risk factors include age ≥ 65 years; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver and/or renal dysfunction; poor performance status; or human immunodeficiency virus (HIV) infection.

x. Patient meets both of the following (a and b):

1. Patient had a neutropenic complication from the previous chemotherapy cycle and did NOT receive prophylaxis with a colony stimulating factor; AND
   Note: Examples of colony stimulating factors include filgrastim products, pegfilgrastim products, and Rolvedon.
2. A reduced dose or frequency of chemotherapy may compromise treatment outcome; AND

G) The medication is prescribed by or in consultation with an oncologist or hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ryzneuta is not recommended in the following situations:

14. Peripheral Blood Progenitor Cell Collection and Therapy. As a limitation of use in the Ryzneuta prescribing information, it is noted that Ryzneuta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.[1]

15. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

41. Ryzneuta® subcutaneous injection [prescribing information]. Singapore: Evive; November 2023.
42. The NCCN Hematopoietic Growth Factors Clinical Practice Guidelines in Oncology (version 2.2024 – December 12, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 12, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Complement Inhibitors – Empaveli Prior Authorization Policy
- Empaveli™ (pegcetacoplan subcutaneous infusion – Apellis)

REVIEW DATE: 05/24/2023

OVERVIEW

Empaveli, a complement C3 inhibitor, is indicated for the treatment of **paroxysmal nocturnal hemoglobinuria** (PNH) in adults.

Disease Overview

PNH is a rare disorder involving bone marrow failure that manifests with hemolytic anemia, thrombosis, and peripheral blood cytopenias.[2-4] Due to the absence of two glycosylphosphatidylinositol (GPI)-anchored proteins, CD55 and CD59, uncontrolled complement activation leads to hemolysis and other PNH manifestations. GPI anchor protein deficiency is often due to mutations in phosphatidylinositol glycan class A (PIGA), a gene involved in the first step of GPI anchor biosynthesis. PNH is a clinical diagnosis that should be confirmed with peripheral blood flow cytometry to detect the absence or severe deficiency of GPI-anchored proteins on at least two lineages.[2-4] Other agents indicated for the management of PNH in adults include Soliris® (eculizumab intravenous infusion) and Ultomiris® (ravulizumab intravenous infusion), both C5 complement inhibitors.[5,6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Empaveli. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Empaveli as well as the monitoring required for adverse events and long-term efficacy, approval requires Empaveli to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Empaveli is recommended in those who meet the following criteria:

FDA-Approved Indication

7. **Paroxysmal Nocturnal Hemoglobinuria.** Approve for the duration noted if the patient meets ONE of the following criteria (A or B):
   - **A)** Initial therapy. Approve for 4 months if the patient meets the following criteria (i, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Paroxysmal nocturnal hemoglobinuria diagnosis was confirmed by peripheral blood flow cytometry results showing the absence or deficiency of glycosylphosphatidylinositol-anchored proteins on at least two cell lineages; AND

iii. For a patient transitioning to Empaveli from Soliris (eculizumab intravenous infusion) or Ultomiris (ravulizumab intravenous infusion), the prescriber attests that these medications will be discontinued within 4 weeks after starting Empaveli; AND

iv. The medication is prescribed by or in consultation with a hematologist.

B) Patient is Currently Receiving Empaveli. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient is continuing to derive benefit from Empaveli according to the prescriber; AND
Note: Examples of benefit include increase in or stabilization of hemoglobin levels, decreased transfusion requirements or transfusion independence, reductions in hemolysis.

iii. The medication is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Empaveli is not recommended in the following situations:

16. **Concurrent Use with Soliris (eculizumab intravenous infusion) or Ultomiris (ravulizumab intravenous infusion) for > 4 weeks.** Concurrent use of Soliris and/or Ultomiris, two C5 inhibitors indicated for use in paroxysmal nocturnal hemoglobinuria for adults, with Empaveli is not recommended. However, to reduce the risk of hemolysis from abrupt treatment discontinuation, patients currently receiving Soliris or Ultomiris and switching to Empaveli may receive these agents concomitantly for no more than 4 weeks after starting Empaveli.

17. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

133. Empaveli™ subcutaneous infusion [prescribing information]. Waltham, MA: Apellis; February 2023.
134. Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med.* 2021;384(11):1028-1037.
135. Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal hemogloinuria. *Hematology Am Soc Hematol Edu Program*. 2016;2016(1):208-216.
136. Roth A, Maciejewski J, Nishinura JI, et al. Screening and diagnostic clinical algorithm for paroxysmal nocturnal hemoglobinuria: Expert consensus. *Eur J Haematol*. 2018;101(1):3-11.
137. Soliris® intravenous infusion [prescribing information]. Boston, MA: Alexion; November 2020.
138. Ultomiris® intravenous infusion [prescribing information]. NewHaven, CT: Alexion; July 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Complement Inhibitors – Fabhalta Prior Authorization Policy
- Fabhalta® (iptacopan capsules – Novartis)

REVIEW DATE: 12/20/2023

OVERVIEW

Fabhalta, a Factor B inhibitor, is indicated for the treatment of **paroxysmal nocturnal hemoglobinuria** (PNH) in adults.

Disease Overview

PNH is a rare disorder involving bone marrow failure that manifests with hemolytic anemia, thrombosis, and peripheral blood cytopenias.[2-4] Due to the absence of two glycosylphosphatidylinositol (GPI)-anchored proteins, CD55 and CD59, uncontrolled complement activation leads to hemolysis and other PNH manifestations. GPI anchor protein deficiency is often due to mutations in phosphatidylinositol glycan class A (PIGA), a gene involved in the first step of GPI anchor biosynthesis. PNH is a clinical diagnosis that should be confirmed with peripheral blood flow cytometry to detect the absence or severe deficiency of GPI-anchored proteins on at least two lineages.[2-4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Fabhalta. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Fabhalt as well as the monitoring required for adverse events and long-term efficacy, approval requires Fabhalt to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Fabhalta is recommended in those who meet the following criteria:

FDA-Approved Indication

8. Paroxysmal Nocturnal Hemoglobinuria. Approve for the duration noted if the patient meets ONE of the following (A or B):

C) Initial therapy. Approve for 4 months if the patient meets the following (i, ii, and iii):
- **v.** Patient is ≥ 18 years of age; AND
- **vi.** Paroxysmal nocturnal hemoglobinuria diagnosis was confirmed by peripheral blood flow cytometry results showing the absence or deficiency of glycosylphosphatidylinositol-anchored proteins on at least two cell lineages; AND
- **vii.** The medication is prescribed by or in consultation with a hematologist.

D) Patient is Currently Receiving Fabhalta. Approve for 1 year if the patient meets the following (i, ii, and iii):
- **iv.** Patient is ≥ 18 years of age; AND

v. Patient is continuing to derive benefit from Fabhalta according to the prescriber; AND
Note: Examples of benefit include increase in or stabilization of hemoglobin levels, decreased transfusion requirements or transfusion independence, reductions in hemolysis.

vi. The medication is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Fabhalta is not recommended in the following situations:

18. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Complement Inhibitors – Veopoz Prior Authorization Policy
- Veopoz™ (pozelimab-bbfg intravenous infusion and subcutaneous injection – Regeneron)

REVIEW DATE: 09/08/2023

OVERVIEW

Veopoz, a complement inhibitor, is indicated for the treatment of CD55-deficient protein-losing enteropathy, also known as CHAPLE disease, in adult and pediatric patients ≥ 1 year of age.[1]

Disease Overview

CHAPLE (which stands for Complement Hyperactivation, Angiopathic thrombosis, and Protein-Losing Enteropathy) disease is an ultra-rare inherited immune disease that causes the complement system to become overactive.[2-5] It is caused by biallelic loss-of-function mutations in the CD55 gene, which leads to loss of protein expression and can result in the complement system attacking the body's own cells. There are fewer than 100 patients diagnosed worldwide with CHAPLE disease; it is estimated to impact around 10 patients in the US. Symptoms can include abdominal pain, nausea, vomiting, diarrhea, loss of appetite, weight loss, impaired growth, and edema. Severe thrombotic vascular occlusions (blockage of blood vessels) can also occur among patients with CHAPLE disease, which can be life-threatening. The condition mainly impacts children, including infants, and is associated with morbidity and a higher risk of mortality.

Dosing Information

Veopoz is administered by a healthcare provider.[1] On Day 1, give a single 30 mg/kg loading dose by intravenous infusion. Day 8 and thereafter, the maintenance dose is 10 mg/kg as a subcutaneous injection once weekly. The maintenance dosage may be increased to 12 mg/kg once weekly if there is inadequate clinical response after at least three weekly doses (starting from Week 4). The maximum maintenance dosage is 800 mg once weekly. Doses exceeding 400 mg require two injections.

Safety

Veopoz has a Boxed Warning regarding serious meningococcal infections.[1] Life-threatening and fatal meningococcal infections have occurred in patients treated with complement inhibitors. Complete or update meningococcal vaccination at least 2 weeks before administering the first dose of Veopoz, unless the risks of delaying therapy outweigh the risks of developing meningococcal infection. Follow the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients receiving a complement inhibitor. Also, patients treated with Veopoz may be at increased risk of developing serious infections due to *Streptococcus pneumonia* and *Haemophilus influenza* type b; administer vaccinations for the prevention of these infections according to ACIP guidelines.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Veopoz. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Veopoz as well as the monitoring required for adverse events and long-term efficacy, approval requires Veopoz to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Veopoz as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory data, genetic tests, and/or other information. Subsequent coverage reviews for a patient who has previously met the documentation requirement for the genetic test criterion in the *Complement Inhibitors – Veopoz Prior Authorization Policy* through the Coverage Review Department and who is requesting reauthorization, do NOT require re-submission of documentation for reauthorization regarding the genetic test criterion.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Veopoz is recommended in those who meet the following criteria:

FDA-Approved Indication

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4. CD55-Deficient Protein-Losing Enteropathy (CHAPLE Disease [Complement Hyperactivation, Angiopathic thrombosis, and Protein-Losing Enteropathy]). Approve for the duration noted below if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following (i, ii, iii, iv, and v):

- **i.** Patient is ≥ 1 year of age; AND
- **ii.** Patient has had a genetic test confirming the diagnosis of CHAPLE disease with a biallelic CD55 loss-of-function mutation **[documentation required]**; AND
- **iii.** Patient meets both of the following (a and b):
  - **a)** Patient has a serum albumin level ≤ 3.2 g/dL **[documentation required]**; AND
  - **b)** According to the prescribing physician, the patient has active disease and is experiencing one or more signs or symptoms within the last 6 months; AND
    Note: Examples of signs and symptoms include abdominal pain, diarrhea, vomiting, peripheral edema, or facial edema.
- **iv.** Patient meets all of the following (a, b, and c):
  - **a)** Patient does not have a of meningococcal infection; AND
  - **b)** Patient has received or is in compliance with updated meningococcal vaccinations according to the most current Advisory Committee on Immunization Practices recommendations; AND
  - **c)** Patient has received or is in compliance with updated vaccinations for the prevention of *Streptococcus pneumonia* and *Haemophilus influenza* type b infections according to the most current Advisory Committee on Immunization Practices guidelines; AND
- **v.** Medication is prescribed by a physician with expertise in managing CHAPLE disease; OR

B) Patient Currently Receiving Veopoz. Approve for 1 year if the patient meets the following (i, ii, iii, and iv):

- **i.** Patient is ≥ 1 year of age; AND
- **ii.** Patient has had a genetic test confirming the diagnosis of CHAPLE disease with a biallelic CD55 loss-of-function mutation **[documentation required]**; AND
- **iii.** Medication is prescribed by a physician with expertise in managing CHAPLE disease; AND
- **iv.** Patient had experienced a response to therapy **[documentation required]**.
  Note: Examples of a response to therapy include increased serum albumin levels, maintenance of serum albumin levels within a normal range, a reduction in albumin transfusions, increases in or maintenance of protein and/or immunoglobulin levels, improvement in clinical outcomes after receipt of therapy (e.g., decreases in the frequency of problematic abdominal pain, bowel movement frequency, facial edema severity, and peripheral edema severity), reduced frequency

in hospitalizations, increase in growth percentiles (e.g., body weight-for age and/or stature-for-age percentiles), and/or reduced use of corticosteroids.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Veopoz is not recommended in the following situations:

19. Concomitant Use with Other Complement Inhibitors. In the pivotal study, use of other complement inhibitors was prohibited.

20. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Complement Inhibitors – Soliris Prior Authorization Policy
- Soliris® (eculizumab intravenous infusion – Alexion)

REVIEW DATE: 09/20/2023

OVERVIEW

Soliris, a complement C5 inhibitor, is indicated for the following uses:[1]

- **Atypical hemolytic uremic syndrome** (aHUS), to inhibit complement-mediated thrombotic microangiopathy.
  Limitation of Use. Soliris is not indicated for the treatment of patients with Shiga toxin *Escherichia coli*-related hemolytic uremic syndrome.
- **Generalized myasthenia gravis** (gMG), in adults who are anti-acetylcholine receptor (AChR) antibody-positive.
- **Neuromyelitis optica spectrum disorder** (NMOSD), in adults who are anti-aquaporin-4 (AQP4) antibody-positive.
- **Paroxysmal nocturnal hemoglobinuria** (PNH), to reduce hemolysis.

The Soliris prescribing information has a Boxed Warning about serious meningococcal infections.[1] Patients should be immunized with a meningococcal vaccine at least 2 weeks prior to the first dose of Soliris, unless the risks of delaying Soliris outweigh the risk of developing a meningococcal infection. Vaccination reduces, but does not eliminate, the risk of meningococcal infections.

Soliris is available only through a restricted access program under a Risk Evaluation and Mitigation Strategy (REMS).[1]

The safety and effectiveness of Soliris for the treatment of PNH, gMG, and NMOSD in pediatric patients have not been established.[1] The safety and effectiveness of Soliris in pediatric patients for aHUS is supported by evidence from four adequate and well-controlled clinical studies assessing the safety and effectiveness of Soliris for the treatment of aHUS.

Disease Overview

Hemolytic uremic syndrome (HUS) is defined as the triad of non-immune hemolytic anemia, thrombocytopenia, and acute renal failure, in which the underlying lesions are mediated by systemic thrombotic microangiopathy.[2] aHUS should be distinguished from a more common condition referred to as typical HUS.[3] aHUS is a sub-type of HUS in which thrombotic microangiopathy is the consequence of endothelial damage in the microvasculature of the kidneys and other organs due to a dysregulation of the activity of the complement system. The typical form is caused by infection with certain strains of *E. coli* bacteria that produce toxic substances called Shiga-like toxins; Soliris is not indicated for the treatment of Shiga toxin *E. coli*-related hemolytic uremic syndrome.[1-3]

Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body, including the arms and legs.[4] The hallmark of MG is muscle weakness that worsens after periods of activity and improves after periods of rest. Acquired MG results from the binding of autoantibodies to components of the neuromuscular junction, most commonly the AChR.[5] Soliris was studied in patients with gMG with anti-

AChR antibodies with a Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV and a Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score ≥ 6.[1]

NMOSD is a rare, relapsing, autoimmune disorder of the brain and spinal cord with optic neuritis and/or myelitis as predominate characteristic symptoms.[6] NMOSD often causes significant, permanent damage to vision and/or spinal cord function resulting in blindness or impaired mobility.[7] Patients may experience pain, paralysis, loss of bowel and bladder control, loss of visual acuity, uncontrolled motor functions, and complications can cause death. Uplizna™ (inebilizumab-cdon intravenous infusion) and Enspryng™ (satralizumab-mwge subcutaneous injection) are two other FDA-approved medications for treatment of NMOSD in adults who are anti-AQP4 antibody-positive.[8,9] For acute attacks, typical treatment is high-dose intravenous corticosteroids.[10,11] Plasma exchange may be effective in patients who suffer acute severe attacks that do not respond to intravenous corticosteroids. For long-term control of the disease, a variety of immunosuppressive drugs are utilized as first-line therapy. While all are considered off-label uses, corticosteroids, azathioprine, mycophenolate mofetil, and rituximab are treatments prescribed as preventative therapy.

PNH is a rare, genetic disorder of hematopoietic stem cells.[12,13] The mutation in the X-linked gene phosphatidylinositol glycan class A (PIGA) results in a deficiency in the glycosylphosphatidylinositol (GPI) protein, which is responsible for anchoring other protein moieties to the surface of the erythrocytes. Loss of anchoring of these proteins causes cells to hemolyze and leads to complications such as hemolytic anemia, thrombosis, and peripheral blood cytopenias. PNH is a clinical diagnosis that should be confirmed with peripheral blood flow cytometry to detect the absence or severe deficiency of GPI-anchored proteins on at least two cell lineages.[12,14] Prior to the availability of Soliris, there was no specific therapy for PNH; only supportive management, in terms of managing the cytopenias and controlling thrombotic risk were available. Supportive measures include platelet transfusion, immunosuppressive therapy for patients with bone marrow failure, use of erythropoietin for anemias, and aggressive anticoagulation.

Guidelines

An international consensus guidance for the management of MG was published in 2016.[5] The guidelines recommend pyridostigmine for the initial treatment in most patients with MG. The ability to discontinue pyridostigmine can indicate that the patient has met treatment goals and may guide the tapering of other therapies. Corticosteroids or immunosuppressant therapy should be used in all patients with MG who have not met treatment goals after an adequate trial of pyridostigmine. Nonsteroidal immunosuppressant agents used in MG include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. It is usually necessary to maintain some immunosuppression for many years, sometimes for life. Plasma exchange and intravenous immunoglobulin can be used as short-term treatments in certain patients. A 2020 update to these guidelines provides new recommendations for methotrexate, rituximab, and Soliris.[15] All recommendations should be considered extensions or additions to recommendations made in the initial international consensus guidance. Oral methotrexate may be considered as a steroid-sparing agent in patients with gMG who have not tolerated or responded to steroid-sparing agents. Rituximab should be considered as an early therapeutic option in patients with anti-muscle specific kinase antibody-positive MG who have an unsatisfactory response to initial immunotherapy. Soliris should be considered in the treatment of severe, refractory, anti-AChR antibody-positive MG.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Soliris. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Soliris as well as the monitoring required for adverse events and long-term efficacy, approval requires Soliris to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Soliris is recommended in those who meet one of the following criteria:

FDA-Approved Indications

9. Atypical Hemolytic Uremic Syndrome. Approve for 1 year if the patient meets the following (A and B):
- **4.** Patient does not have Shiga toxin *Escherichia coli*-related hemolytic uremic syndrome; AND
- **5.** The medication is being prescribed by or in consultation with a nephrologist.

10. Generalized Myasthenia Gravis. Approve for the duration noted if the patient meets ONE of the following (A or B):

B) Initial therapy. Approve for 6 months if the patient meets the following (i, ii, iii, iv, v, vi, and vii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has confirmed anti-acetylcholine receptor antibody-positive generalized myasthenia gravis; AND
- **iii.** Patient meets both of the following (a and b):
  - **a)** Myasthenia Gravis Foundation of America classification of II to IV; AND
  - **b)** Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 6; AND
- **iv.** Patient meets one of the following (a or b):
  - **a)** Patient received or is currently receiving pyridostigmine; OR
  - **b)** Patient has had inadequate efficacy, a contraindication, or significant intolerance to pyridostigmine; AND
- **v.** Patient meets one of the following (a or b):
  - **a)** Patient received or is currently receiving two different immunosuppressant therapies for ≥ 1 year; OR
  - **b)** Patient had inadequate efficacy, a contraindication, or significant intolerance to two different immunosuppressant therapies; AND
    Note: Examples of immunosuppressant therapies tried include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus, and cyclophosphamide.
- **vi.** Patient has evidence of unresolved symptoms of generalized myasthenia gravis; AND
  Note: Evidence of unresolved symptoms of generalized myasthenia gravis includes difficulty swallowing, difficulty breathing, and a functional disability resulting in the discontinuation of physical activity (e.g., double vision, talking, impairment of mobility).
- **vii.** The medication is being prescribed by or in consultation with a neurologist.

C) Patient is Currently Receiving Soliris. Approve for 1 year if the patient meets the following (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient is continuing to derive benefit from Soliris, according to the prescriber; AND
  Note: Examples of derived benefit include reductions in exacerbations of myasthenia gravis; improvements in speech, swallowing, mobility, and respiratory function.

iii. The medication is being prescribed by or in consultation with a neurologist.

11. Neuromyelitis Optica Spectrum Disorder. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 year if the patient meets the following (i, ii, iii, iv, and v):

i. Patient is ≥ 18 years of age; AND

ii. Diagnosis was confirmed by a positive blood serum test for anti-aquaporin-4 antibody; AND

iii. Patient is currently receiving or has previously tried two of the following systemic therapies (a, b, c, or d):

a) Azathioprine; OR

b) Corticosteroid; OR

c) Mycophenolate mofetil; OR

d) Rituximab; AND

Note: An exception to the requirement for a trial of a systemic therapy can be made if the patient has already tried Enspryng (satralizumab-mwge subcutaneous injection) or Uplizna (inebilizumab-cdon intravenous infusion) for neuromyelitis optica spectrum disorder (NMOSD). Patients who have already tried Enspryng or Uplizna for NMOSD are not required to try another systemic agent.

iv. Patient has a of at least one relapse in the last 12 months or two relapses in the last 2 years; AND

v. The medication is being prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Soliris. Approve for 1 year if the patient meets the following criteria (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Diagnosis was confirmed by a positive blood serum test for anti-aquaporin-4 antibody; AND

iii. According to the prescriber, patient has had clinical benefit from the use of Soliris; AND
Note: Examples of clinical benefit include reduction in relapse rate, reduction in symptoms (e.g., pain, fatigue, motor function), and a slowing progression in symptoms.

iv. The medication is being prescribed by or in consultation with a neurologist.

12. Paroxysmal Nocturnal Hemoglobinuria. Approve for the duration noted if the patient meets ONE of the following (A or B):

E) Initial therapy. Approve for 6 months if the patient meets the following (i, ii, and iii):

viii. Patient is ≥ 18 years of age; AND

ix. Diagnosis was confirmed by peripheral blood flow cytometry results showing the absence or deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins on at least two cell lineages; AND

x. The medication is being prescribed by or in consultation with a hematologist.

B) Patient is Currently Receiving Soliris. Approve for 1 year if the patient meets the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient is continuing to derive benefit from Soliris, according to the prescriber; AND
Note: Examples of derived benefit include stabilization of hemoglobin levels, decreased transfusion requirements or transfusion independence, reductions in hemolysis.

iii. The medication is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Soliris is not recommended in the following situations:

21. **Concomitant Use with a Rituximab Product, a Neonatal Fc Receptor Blocker, Enspryng (satralizumab-mwge subcutaneous [SC] injection), Ultomiris (ravulizumab-cwzy intravenous [IV] infusion or SC injection), or Uplizna (inebilizumab-cdon IV infusion)**. There is no evidence to support concomitant use of Soliris with a rituximab product, a neonatal Fc receptor blocker, Enspryng, Ultomiris, or Uplizna.
    Note: Examples of Neonatal Fc receptor blockers are: Vyvgart (efgartigimod alfa-fcab IV infusion), Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc SC injection), and Rystiggo [rozanolixizumab-noli SC infusion).

22. **Concomitant Use with Empaveli > 4 Weeks.** Concomitant use of Soliris with Empaveli is not recommended. However, to reduce the risk of hemolysis from abrupt treatment discontinuation in a patient switching from Soliris to Empaveli, patient should use both therapies for 4 weeks; after which, Soliris is discontinued and patient is continued on Empaveli monotherapy.

23. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Complement Inhibitors – Ultomiris Intravenous Prior Authorization Policy
- Ultomiris® (ravulizumab-cwvz intravenous infusion – Alexion)

REVIEW DATE: 09/20/2023

OVERVIEW

Ultomiris intravenous, a complement inhibitor, is indicated for the following uses:[1]

- **Atypical hemolytic uremic syndrome** (aHUS), to inhibit complement-mediated thrombotic microangiopathy in patients ≥ one month of age.
  Limitation of use: Ultomiris IV is not indicated for the treatment of patients with Shiga toxin *Escherichia coli*-related hemolytic uremic syndrome.
  - **Generalized myasthenia gravis** (gMG), in adults who are anti-acetylcholine receptor (AChR) antibody-positive.
- **Paroxysmal nocturnal hemoglobinuria** (PNH), in patients ≥ one month of age.

Ultomiris is also available in a subcutaneous formulation that is indicated for maintenance therapy of aHUS and PNH in adults.[1]

The Ultomiris prescribing information has a Boxed Warning about serious meningococcal infections.[1] Patients should be immunized with a meningococcal vaccine at least 2 weeks prior to the first dose of Ultomiris, unless the risks of delaying Ultomiris outweigh the risk of developing a meningococcal infection. Vaccination reduces, but does not eliminate, the risk of meningococcal infections.

Ultomiris is available only through a restricted access program called Ultomiris Risk Evaluation and Mitigation Strategy (REMS).[1]

Disease Overview

Hemolytic uremic syndrome (HUS) is defined as the triad of non-immune hemolytic anemia, thrombocytopenia, and acute renal failure, in which the underlying lesions are mediated by systemic thrombotic microangiopathy.[2] aHUS should be distinguished from a more common condition referred to as typical HUS.[3] aHUS is a sub-type of HUS in which thrombotic microangiopathy is the consequence of endothelial damage in the microvasculature of the kidneys and other organs due to a dysregulation of the activity of the complement system. The typical form is caused by infection with certain strains of *E. coli* bacteria that produce toxic substances called Shiga-like toxins; Ultomiris IV is not indicated for the treatment of Shiga toxin *E. coli*-related hemolytic uremic syndrome.[1,3]

Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body, including the arms and legs.[4] The hallmark of MG is muscle weakness that worsens after periods of activity and improves after periods of rest. Acquired MG results from the binding of autoantibodies to components of the neuromuscular junction, most commonly the AChR.[5] Ultomiris IV was studied in patients with gMG with anti-AChR antibodies with a Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV, and a Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score ≥ 6.[1]

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, genetic disorder of hematopoietic stem cells.[6,7] The mutation in the X-linked gene phosphatidylinositol glycan class A (PIGA) results in a deficiency in the

glycosylphosphatidylinositol (GPI) protein, which is responsible for anchoring other protein moieties to the surface of the erythrocytes. Loss of anchoring of these proteins causes cells to hemolyze and leads to complications such as hemolytic anemia, thrombosis, and peripheral blood cytopenias. PNH is a clinical diagnosis that should be confirmed with peripheral blood flow cytometry to detect the absence or severe deficiency of GPI-anchored proteins on at least two lineages.[6,8] Prior to the availability of Soliris, there was no specific therapy for PNH; only supportive management, in terms of managing the cytopenias and controlling thrombotic risk were available. Supportive measures include platelet transfusion, immunosuppressive therapy for patients with bone marrow failure, use of erythropoietin for anemias, and aggressive anticoagulation.

Guidelines

An international consensus guidance for the management of MG was published in 2016.[5] The guidelines recommend pyridostigmine for the initial treatment in most patients with MG. The ability to discontinue pyridostigmine can indicate that the patient has met treatment goals and may guide the tapering of other therapies. Corticosteroids or immunosuppressant therapy should be used in all patients with MG who have not met treatment goals after an adequate trial of pyridostigmine. Nonsteroidal immunosuppressant agents used in MG include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. It is usually necessary to maintain some immunosuppression for many years, sometimes for life. Plasma exchange and intravenous immunoglobulin can be used as short-term treatments in certain patients. A 2020 update to these guidelines provides new recommendations for methotrexate, rituximab, and Soliris.[9] All recommendations should be considered extensions or additions to recommendations made in the initial international consensus guidance. Oral methotrexate may be considered as a steroid-sparing agent in patients with gMG who have not tolerated or responded to steroid-sparing agents. Rituximab should be considered as an early therapeutic option in patients with anti-muscle specific kinase antibody-positive MG who have an unsatisfactory response to initial immunotherapy. Soliris should be considered in the treatment of severe, refractory, anti-AChR antibody-positive gMG.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ultomiris intravenous. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ultomiris intravenous as well as the monitoring required for adverse events and long-term efficacy, approval requires Ultomiris intravenous to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ultomiris intravenous is recommended in those who meet one of the following criteria:

FDA-Approved Indications

13. **Atypical Hemolytic Uremic Syndrome.** Approve for 1 year if the patient meets the following (A and B):
    6. Patient does not have Shiga toxin *Escherichia coli*-related hemolytic uremic syndrome; AND
    7. The medication is prescribed by or in consultation with a nephrologist.

14. Generalized Myasthenia Gravis. Approve for the duration noted if the patient meets ONE of the following (A or B):

D) Initial therapy. Approve for 6 months if the patient meets the following (i, ii, iii, iv, v, vi, and vii):

viii. Patient is ≥ 18 years of age; AND

ix. Patient has confirmed anti-acetylcholine receptor antibody-positive generalized myasthenia gravis; AND

x. Patient meets both of the following (a and b):

a) Myasthenia Gravis Foundation of America classification of II to IV; AND

b) Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 6; AND

xi. Patient meets one of the following (a or b):

a) Patient received or is currently receiving pyridostigmine; OR

b) Patient has had inadequate efficacy, a contraindication, or significant intolerance to pyridostigmine; AND

xii. Patient meets one of the following (a or b):

a) Patient received or is currently receiving two different immunosuppressant therapies for ≥ 1 year; OR

b) Patient had inadequate efficacy, a contraindication, or significant intolerance to two different immunosuppressant therapies; AND

Note: Examples of immunosuppressant therapies include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus, and cyclophosphamide.

xiii. Patient has evidence of unresolved symptoms of generalized myasthenia gravis; AND

Note: Evidence of unresolved symptoms of generalized myasthenia gravis includes difficulty swallowing, difficulty breathing, or a functional disability resulting in the discontinuation of physical activity (e.g., double vision, talking, impairment of mobility).

xiv. The medication is being prescribed by or in consultation with a neurologist.

E) Patient is Currently Receiving Ultomiris intravenous. Approve for 1 year if the patient meets the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient is continuing to derive benefit from Ultomiris intravenous, according to the prescriber; AND

Note: Examples of derived benefit include reductions in exacerbations of myasthenia gravis; improvements in speech, swallowing, mobility, and respiratory function.

iii. The medication is being prescribed by or in consultation with a neurologist.

15. Paroxysmal Nocturnal Hemoglobinuria. Approve for the duration noted if the patient meets ONE of the following (A or B):

F) Initial therapy. Approve for 6 months if the patient meets the following (i and ii):

iv. Diagnosis was confirmed by peripheral blood flow cytometry results showing the absence or deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins on at least two cell lineages; AND

v. The medication is prescribed by or in consultation with a hematologist.

G) Patient is Currently Receiving Ultomiris (intravenous or subcutaneous). Approve for 1 year if the patient meets the following (i and ii):

a. Patient is continuing to derive benefit from Ultomiris (intravenous or subcutaneous), according to the prescriber.

Note: Examples of benefit from Ultomiris (intravenous or subcutaneous) include stabilization of hemoglobin levels, decreased transfusion requirements or transfusion independence, reductions in hemolysis.

ii. The medication is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ultomiris intravenous is not recommended in the following situations:

1. **Concomitant Use with Another Complement Inhibitor, a Rituximab Product, or a Neonatal Fc Receptor Blocker**. There is no evidence to support concomitant use of Ultomiris intravenous with another complement inhibitor, a rituximab product, or a neonatal Fc receptor blocker.
   Note: Examples of complement inhibitors are Empaveli (pegcetacoplan subcutaneous [SC] infusion and Soliris (eculizumab intravenous [IV] infusion).
   Note: Examples of neonatal Fc receptor blockers are Vyvgart (efgartigimod alfa-fcab IV infusion], Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc SC injection), and Rystiggo (rozanolixizumab-noli SC infusion).

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Complement Inhibitors – Ultomiris Subcutaneous Prior Authorization Policy
- Ultomiris® (ravulizumab-cwvz subcutaneous injection – Alexion)

REVIEW DATE: 08/02/2023

OVERVIEW

Ultomiris subcutaneous, a complement inhibitor, is indicated for the following uses:[1]
- **Atypical hemolytic uremic syndrome** (aHUS), for maintenance in adults.
- **Paroxysmal nocturnal hemoglobinuria** (PNH), for maintenance in adults.

Ultomiris is also available in an intravenous formulation that is indicated for aHUS, generalized myasthenia gravis, and PNH.[1] Prior to initiation of Ultomiris subcutaneous, a loading dose of Ultomiris intravenous must be administered. Ultomiris subcutaneous is available as a 245 mg single-dose, prefilled cartridge for use with an on-body injector and is not approved for use in pediatric patients.

Disease Overview

Hemolytic uremic syndrome (HUS) is defined as the triad of non-immune hemolytic anemia, thrombocytopenia, and acute renal failure, in which the underlying lesions are mediated by systemic thrombotic microangiopathy.[2] aHUS is a subtype of HUS in which thrombotic microangiopathy is the consequence of endothelial damage in the microvasculature of the kidneys and other organs due to a dysregulation of the activity of the complement system. Various aHUS-related mutations have been identified in genes of the complement system, which can explain approximately 60% of the aHUS cases, and a number of mutations and polymorphisms have been functionally characterized. aHUS should be distinguished from a more common condition referred to as typical HUS.[3] The two disorders have different causes and different signs and symptoms. Unlike aHUS, the typical form is caused by infection with certain strains of *Escherichia coli* bacteria that produce toxic substances called Shiga-like toxins. The typical form is characterized by severe diarrhea and most often affects children < 10 years of age, and it is less likely than aHUS to involve recurrent attacks of kidney damage that lead to end stage renal disease. The incidence of aHUS is estimated to be 1:500,000 people/year in the US; aHUS is approximately 10 times less common than typical HUS.

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, genetic disorder of hematopoietic stem cells.[4,5] The mutation in the X-linked gene phosphatidylinositol glycan class A (PIGA) results in a deficiency in the glycosylphosphatidylinositol (GPI) protein, which is responsible for anchoring other protein moieties to the surface of the erythrocytes. Loss of anchoring of these proteins causes cells to hemolyze and leads to complications such as hemolytic anemia, thrombosis, and peripheral blood cytopenias. PNH is a clinical diagnosis that should be confirmed with peripheral blood flow cytometry to detect the absence or severe deficiency of GPI-anchored proteins on at least two lineages.[4,8] Prior to the availability of Soliris, there was no specific therapy for PNH; only supportive management, in terms of managing the cytopenias and controlling thrombotic risk were available. Supportive measures include platelet transfusion, immunosuppressive therapy for patients with bone marrow failure, use of erythropoietin for anemias, and aggressive anticoagulation.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Ultomiris subcutaneous. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ultomiris subcutaneous as well as the monitoring required for adverse events and long-term efficacy, approval requires Ultomiris subcutaneous to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Ultomiris subcutaneous is recommended in those who meet one of the following criteria:

FDA-Approved Indications

16. Atypical Hemolytic Uremic Syndrome. Approve for 1 year if the patient meets the following (A, B, C, and D):
- **8.** Patient is ≥ 18 years of age; AND
- **9.** Patient does not have Shiga toxin *E. coli* related hemolytic uremic syndrome; AND
- **10.** Patient has received or will receive Ultomiris intravenous infusion loading dose prior to initiation of Ultomiris subcutaneous; AND
- **11.** The medication is prescribed by or in consultation with a nephrologist.

17. Paroxysmal Nocturnal Hemoglobinuria. Approve for the duration noted if the patient meets ONE of the following (A or B):

H) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, and iv):
- **vi.** Patient is ≥ 18 years of age; AND
- **vii.** Diagnosis was confirmed by peripheral blood flow cytometry results showing the absence or deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins on at least two cell lineages; AND
- **viii.** Patient has received or will receive Ultomiris intravenous infusion loading dose prior to initiation of Ultomiris subcutaneous; AND
- **ix.** The medication is prescribed by or in consultation with a hematologist.

I) Patient is Currently Receiving Ultomiris (intravenous or subcutaneous). Approve for 1 year if the patient meets the following (i, ii, iii, and iv):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has been established on therapy for at least 6 months; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).
- **iii.** Patient is continuing to derive benefit from Ultomiris (intravenous or subcutaneous), according to the prescriber.
  Note: Examples of benefit from Ultomiris (intravenous or subcutaneous) include stabilization of hemoglobin levels, decreased transfusion requirements or transfusion independence, reductions in hemolysis.
- **iv.** The medication is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ultomiris subcutaneous is not recommended in the following situations:

3. **Concurrent Use with another Complement Inhibitor.** Concurrent use with other complement inhibitors (e.g., Empaveli [pegcetacoplan subcutaneous infusion], Soliris [eculizumab intravenous infusion], or Ultomiris intravenous) is not recommended with Ultomiris subcutaneous.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Complement Inhibitors – Zilbrysq Prior Authorization Policy
- Zilbrysq® (zilucoplan subcutaneous injection – UCB)

REVIEW DATE: 11/01/2023

OVERVIEW

Zilbrysq, a complement C5 inhibitor, is indicated for the treatment of generalized myasthenia gravis in adults who are anti-acetylcholine receptor antibody-positive.[1]

Disease Overview

Myasthenia gravis is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body, including the arms and legs.[2] The hallmark of myasthenia gravis is muscle weakness that worsens after periods of activity and improves after periods of rest. Certain muscles such as those that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are often involved in the disorder; however, the muscles that control breathing and neck and limb movements may also be affected. Acquired myasthenia gravis results from the binding of autoantibodies to components of the neuromuscular junction, most commonly the acetylcholine receptor.[3]

Clinical Efficacy

The efficacy of Zilbrysq was evaluated in 12-week, multicenter, randomized, double-blind placebo-controlled study (n = 174).[1,4] All of the enrolled patients had anti-acetylcholine receptor antibody-positive generalized myasthenia gravis. In addition, patients had a Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV and a Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score of ≥ 6. MG-ADL assesses the impact of generalized myasthenia gravis on daily functions of eight signs or symptoms that are typically impacted by this disease. Each sign or symptom is assessed on a 4-point scale; a higher score indicates greater impairment. At baseline, 85% of patients in each group received cholinesterase inhibitors, 63% received steroids, and 51% received non-steroidal immunosuppressive therapies, at stable doses. Patients were randomized to receive either Zilbrysq 0.3 mg/kg or placebo. The primary efficacy endpoint was a comparison of the change from baseline between treatment groups in the MG-ADL total score at Week 12. Statistically significantly greater improvement in the MG-ADL total score was observed in the Zilbrysq group compared with placebo: -4.39 points vs. -2.30 points, respectively ($P < 0.001$). Statistically significant improvement in the secondary efficacy endpoints were also observed in the Zilbrysq group vs. placebo.

Guidelines

An international consensus guidance for the management of myasthenia gravis was published in 2016.[3] The guidelines recommend pyridostigmine for the initial treatment in most patients with myasthenia gravis. The ability to discontinue pyridostigmine can indicate that the patient has met treatment goals and may guide the tapering of other therapies. Corticosteroids or immunosuppressant therapy should be used in all patients with myasthenia gravis who have not met treatment goals after an adequate trial of pyridostigmine. Nonsteroidal immunosuppressant agents used in treatment of myasthenia gravis include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. It is usually necessary to maintain some immunosuppression for many years, sometimes for life. Plasma exchange and intravenous immunoglobulin can be used as short-term treatments in certain patients. A 2020 update to these guidelines provides new/additional recommendations for methotrexate, rituximab, and Soliris® (eculizumab

intravenous infusion).[5] All recommendations should be considered extensions or additions to recommendations made in the initial international consensus guidance (2016). Oral methotrexate may be considered as a steroid-sparing agent in patients with generalized myasthenia gravis who have not tolerated or responded to steroid-sparing agents. Rituximab should be considered as an early therapeutic option in patients with anti-muscle-specific tyrosine kinase antibody-positive myasthenia gravis who have an unsatisfactory response to initial immunotherapy. Soliris should be considered in the treatment of severe, refractory, anti-acetylcholine receptor antibody-positive MG.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zilbrysq. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zilbrysq as well as the monitoring required for adverse events and long-term efficacy, approval requires Zilbrysq to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zilbrysq is recommended in those who meet the following criteria:

FDA-Approved Indication

18. Generalized Myasthenia Gravis. Approve for the duration noted if the patient meets ONE of the following (A or B):

F) Initial therapy. Approve for 6 months if the patient meets the following (i, ii, iii, iv, v, vi, and vii):

xv. Patient is ≥ 18 years of age; AND

xvi. Patient has confirmed anti-acetylcholine receptor antibody-positive generalized myasthenia gravis; AND

xvii. Patient meets both of the following (a and b):

a) Myasthenia Gravis Foundation of America classification of II to IV; AND

b) Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 6; AND

xviii. Patient meets one of the following (a or b):

a) Patient received or is currently receiving pyridostigmine; OR

b) Patient has had inadequate efficacy, a contraindication, or significant intolerance to pyridostigmine; AND

xix. Patient meets one of the following (a or b):

a) Patient received or is currently receiving two different immunosuppressant therapies for ≥ 1 year; OR

b) Patient had inadequate efficacy, a contraindication, or significant intolerance to two different immunosuppressant therapies; AND

Note: Examples of immunosuppressant therapies tried include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus, and cyclophosphamide.

xx. Patient has evidence of unresolved symptoms of generalized myasthenia gravis; AND

Note: Evidence of unresolved symptoms of generalized myasthenia gravis includes difficulty swallowing, difficulty breathing, and a functional disability resulting in the discontinuation of physical activity (e.g., double vision, talking, impairment of mobility).

xxi. The medication is being prescribed by or in consultation with a neurologist.

G) Patient is Currently Receiving Zilbrysq. Approve for 1 year if the patient meets the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient is continuing to derive benefit from Zilbrysq, according to the prescriber; AND
Note: Examples of derived benefit include reductions in exacerbations of myasthenia gravis; improvements in speech, swallowing, mobility, and respiratory function.

iii. The medication is being prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zilbrysq is not recommended in the following situations:

5. **Concomitant Use with Another Complement Inhibitor, a Neonatal Fc Receptor Blocker, or a Rituximab Product.** There is no evidence to support concomitant use of Zilbrysq with another complement inhibitor, a neonatal Fc receptor blocker, or a rituximab product.
   F) Note: Examples of complement inhibitors are Soliris (eculizumab intravenous infusion) and Ultomiris (ravulizumab-cwvz intravenous infusion or subcutaneous injection).
   G) Note: Examples of Neonatal Fc receptor blockers are Rystiggo [rozanolixizumab-noli subcutaneous infusion) Vyvgart (efgartigimod alfa-fcab intravenous infusion), and Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection).
   H)
6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Compounded Select Topical Medications Prior Authorization Policy

        - topical ketamine
        - topical gabapentin
        - topical diclofenac
        - topical ketoprofen
        - topical flurbiprofen
- topical nabumetone
- topical meloxicam
- topical hyaluronic acid
- topical mometasone furoate
  topical fluticasone propionate

OVERVIEW

Compounded products are used for a **variety of indications from treating pain to hormone therapy**. The compounded formulations can contain just one active drug in a base vehicle or they may contain a combination of active drugs. Compounded medications are not FDA-approved, thus the FDA has limited regulatory authority over compounding pharmacies since they are licensed by their respective state board of pharmacy. Compounded medications also do not undergo the rigorous drug review process to demonstrate safe and effective use in patients that all commercially available prescription drugs must establish prior to widespread availability. Also, compounded medications generally do not have standardized dosages and duration for use; likewise, there are no standardized protocols to prepare each compound. For these reasons, compounded preparations are at a greater propensity to have batch-to-batch variability and the product sterility/purity cannot be guaranteed relative to the commercially available products.

Clinical Efficacy

There are very limited published controlled studies with established safety and efficacy data supporting use of compounded medications for any condition. The available efficacy data for the targeted topical compounds in this policy are described below.

Topical Ketamine

There are four randomized, placebo-controlled studies published assessing the use of compounded topical ketamine for neuropathic pain. *Study 1* enrolled patients (n = 208) with chemotherapy-induced peripheral neuropathy and randomized them to either a placebo gel or a compounded mixture containing baclofen 10 mg, amitriptyline 40 mg, and ketamine 20 mg in a pluronic lecithin organogel vehicle base.[1] Patients applied the gel twice daily for 4 weeks. There was a trend towards improvement in the sensory neuropathy scale (primary endpoint) compared with placebo, though it was not statistically significant (P = 0.053). Statistically significant improvement was noted with the motor subscale (P = 0.021). *Study 2* enrolled patients (n = 92) with mixed neuropathic pain (i.e., diabetic neuropathy [n = 20/92], postherpetic neuralgia [n = 14/92], post-surgical/post-traumatic neuropathic pain [n = 58/92] with allodynia, hyperalgesia, or pinprick hyperthesia) and evaluated the application of one of four topical creams: topical amitriptyline 2%, topical ketamine 1%, a combination of topical amitriptyline 2% and topical ketamine 1%, or placebo (vehicle base).[2] Patients applied 4 mL cream to the site of maximum pain three times daily (TID) for 3 weeks. Pain levels at the end of the study compared with baseline were not statistically significant between treatment groups. *Study 3* evaluated the efficacy of topical ketamine 5% cream applied TID for 4 weeks in patients (n = 17) with diabetic neuropathy.[3] Seven different pain characteristics (i.e., intensity, sharpness, cold, hot, dull, sensitive, and itchy) were measured using a pain scale both before and after treatment. Diabetic pain measures were reduced in both treatment groups and the placebo effect was equally as strong as ketamine 5% cream. *Study 4* was a cross-over trial that assessed the efficacy of (S)-ketamine 1% ointment or placebo applied four times daily for 15 days in patients (n = 12) with postherpetic neuralgia.[4] There was a wash-out period of 7 days in-between crossover. A numerical verbal scale was used to assess pain scores and efficacy of therapy during three different clinic visits. There was no statistical significance in pain scores during treatments with (S)-ketamine 1% ointment or placebo.

One small randomized, double-blind, placebo-controlled study assessed the use of compounded topical ketamine in patients (n = 20) with complex regional pain syndrome (CRPS).[5] CRPS has been described as a challenging pain syndrome usually starting after a trauma or surgery.[6] CRPS can be classified into two types: patients with CRPS type 1 do not have demonstrable nerve lesions and type 2 is based on objective nerve damage, most commonly caused by severe trauma. CRPS type 1 has also been recognized as a

chronic neuropathic pain syndrome that typically develops in an extremity after tissue trauma. The above mentioned study[5] concluded that topical ketamine did not lead to pain reduction in patients with CRPS, but it did reduce allodynia to brushing.

Topical Gabapentin

There are no published data available with the use of compounded topical gabapentin for neuropathic pain.

The only published trial available is a retrospective study assessing the use of topical gabapentin 2% to 6% cream in women (n = 51) with vulvodynia (chronic, unexplained vulvar pain or discomfort, characterized by burning, stinging, irritation or rawness).[7] After a minimum of 8 weeks of therapy with application of gabapentin cream TID, about 80% of the patients demonstrated at least a 50% improvement in their pain scores. The American College of Obstetricians and Gynecologist committee opinion (2016) [reaffirmed 2018] on persistent vulvar pain mention gabapentin oral as a therapy option, but do not mention compounded gabapentin.[8]

Topical Hyaluronic Acid Sodium Salt

I) Hyaluronic acid is a naturally occurring polysaccharide that is widely distributed in various body tissues.[9] Sodium hyaluronate and other derivatives are used for a variety of conditions, such as osteoarthritis (OA), and as surgical aid in ophthalmic procedures. It is available commercially as FDA-approved products in various dosage forms: as intra-articular injections (e.g., Synvisc®) for the treatment of knee OA; as ophthalmic solution for irrigation (e.g., Vitrax®); and as topical spray, cream, and gel products for use in wound care (e.g., Hylase® wound gel, Bionect® topical gel, cream, spray). There are also multiple hyaluronic acid products available as intradermal injectable gel for use as wrinkle fillers in cosmetic procedures (e.g., Juvederm® XC). Most of the hyaluronic acid products were approved as devices by the FDA.

J)

K) There are limited published data available with the use of compounded topical hyaluronic acid as vaginal suppositories for the treatment of vaginal atrophy in postmenopausal women.[10-14] According to the North American Menopause Society position statement on genitourinary syndrome of menopause (2020), there is no evidence that products with hyaluronic acid have a greater benefit than nonhyaluronic acid vaginal lubricants or moisturizers.[15]

L)

Topical Corticosteroids – Fluticasone Propionate, Mometasone Furoate

M) Fluticasone propionate and mometasone furoate are corticosteroids which are used intranasally for the treatment of allergic and non-allergic rhinitis, by oral inhalation for the treatment of asthma and/or chronic obstructive pulmonary disease (COPD), and as topical preparations for the treatment of inflammatory and pruritic types of dermatoses and psoriasis.[9] These two corticosteroids are available as FDA-approved, commercial products in the following strengths and dosage form: fluticasone propionate 0.05% cream, lotion, and as 0.005% ointment; mometasone furoate 0.1% cream, lotion (topical solution), and ointment.

N)

O) There are no published clinical trial data available for the use of compounded topical formulations of fluticasone propionate or mometasone furoate either alone or in combination with other products for the treatment of skin conditions. One small open-label study (n = 23) evaluated the use of intranasal irrigation of fluticasone propionate in post-endoscopic sinus surgery patients with chronic rhinosinusitis.[16] The main intent of this study was to assess the effects of fluticasone on adrenal function (whether or not it was suppressed) and its effect on intraocular pressure (IOP). The irrigation solution was prepared by emptying a 3-mg capsule of fluticasone propionate (provided by a compounding pharmacy) into 240 mL isotonic saline solution (available OTC as Sinus Rinse™ saline rinse kit) and used twice daily for 6 weeks. There were no significant changes with fluticasone irrigation use in measured salivary cortisol levels or IOP after 6 weeks. No other efficacy data are noted in this study.

P)

Topical Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

The other compounded topical drugs targeted in this policy – topical diclofenac, ketoprofen, flurbiprofen, meloxicam, and nabumetone – all belong to the NSAID drug class. These agents are generally used for the treatment of pain (e.g., OA, musculoskeletal pain). There are several topical NSAID formulations that are FDA-approved and commercially available. Topical diclofenac is commercially available as diclofenac sodium 3% gel, Voltaren® Arthritis over-the-counter (OTC) 1% gel, diclofenac 1.5% and 2% topical solution, diclofenac 0.1% ophthalmic solution, diclofenac epolamine 1.3 % topical patch (Flector®), and Licart® topical patch .[17-21,26] OTC Voltaren Arthritis gel is for the temporary relief of arthritis pain, and diclofenac topical solution is indicated for the treatment of OA of the knees.[18,19] Topical flurbiprofen is commercially available as a 0.03% ophthalmic solution and it is indicated for the treatment of intraoperative miosis.[22] The American College of Rheumatology (ACR) guidelines (2019) for hand, hip, and knee OA recommend topical NSAIDs for the treatment of hand and knee OA.[23] As there multiple FDA-approved topical NSAIDs, the guidelines do not address compounded products.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of the following compounded topical medications: ketamine, gabapentin, diclofenac, ketoprofen, flurbiprofen, meloxicam, nabumetone, hyaluronic acid derivatives, mometasone furoate, and fluticasone propionate. Due to the lack of robust clinical efficacy and safety data, in addition to the lack of standardized dosages and formulations, **approval is not recommended for any condition** for these non-FDA-approved topical compounded formulations of ketamine, gabapentin, diclofenac, ketoprofen, flurbiprofen, meloxicam, nabumetone, hyaluronic acid derivatives, mometasone furoate, and fluticasone propionate (either alone or in combination with other medications).

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of compounded topical formulations of ketamine, gabapentin, diclofenac, ketoprofen, flurbiprofen, meloxicam, nabumetone, hyaluronic acid derivatives, mometasone furoate, and fluticasone propionate (either alone or in combination with other medications) is not recommended in the following situations:

Topical Ketamine

61. Neuropathic Pain. There are published data available from four randomized, placebo-controlled studies assessing the efficacy of compounded topical ketamine, either alone or in combination with other agents (e.g., amitriptyline, baclofen) for the treatment of various types of neuropathic pain (e.g., peripheral neuropathy, diabetic neuropathy).[1-4] In summary, three of the four studies did not show any statistically significant efficacy differences compared with placebo. One study showed a trend towards improvement compared with placebo in patients with CIPN.[1] All of the other published data with topical ketamine use for neuropathic pain are based on case reports, open-label studies, or pilot studies.

62. Complex regional pain syndrome (CRPS). There are very limited published efficacy data available with topical ketamine for the treatment of CRPS. One small double-blind, placebo-controlled study assessed the efficacy of ketamine 10% cream in patients (n = 20) with CRPS type 1 (n = 18/20) and type 2 (n = 2/20) on two separate occassions.[5] The primary aim was to determine whether topical ketamine inhibited sensory disturbances in the symptomatic limb of patients. Topical ketamine did not lead to pain reduction, but allodynia to brushing the skin was reduced. Most of the other published evidence for topical ketamine use for CRPS is based on case reports.

Topical Gabapentin

1. **Neuropathic Pain.** There are no published efficacy or safety data available with compounded topical formulations of gabapentin either alone or in combination with other drugs for use in neuropathic pain.

Q)

2. **Complex regional pain syndrome (CRPS).** There are no published efficacy or safety data available with topical gabapentin use for the treatment of CRPS.

R)

3. **Vulvodynia.** There is one retrospective study that assessed the efficacy of topical gabapentin 2% to 6% in women (n = 51) with vulvodynia.[7] Though topical gabapentin was effective in reducing pain in about 80% of women, these data are limited by small sample size and study design. Large randomized trials are needed to establish the efficacy of topical gabapentin for vulvodynia.

S)

T) Topical NSAIDs (diclofenac, ketoprofen, flurbiprofen, nabumetone, and meloxicam)

1. **Arthritis (e.g., osteoarthritis [OA], rheumatoid arthritis [RA]).** There are no published data available with the use of compounded, non-FDA approved topical formulations of NSAIDs such as topical diclofenac, topical ketoprofen, topical meloxicam, topical nabumetone, or topical flurbiprofen, either alone or in combination with other agents for the treatment of arthritis, such as OA. FDA-approved, commercially available topical NSAIDs such as Voltaren 1% gel, and Pennsaid 1.5% topical solution are indicated for the treatment of OA and have substantial efficacy and safety data supporting their use.[10-11] With the availability of effective and safe FDA-approved topical NSAIDs, the use of other compounded topical NSAIDs with no established efficacy and safety data is not recommended.

U) Topical Fluticasone Propionate and Mometasone Furoate

V) 1. Use in various types of skin conditions (e.g., dermatitis, wound care). There are very limited to no published efficacy or safety data available with non-FDA approved, compounded formulations of fluticasone and mometasone for the treatment of skin conditions.

2. **Cosmetic Use (e.g., scar therapy, for minimizing stretch marks).** Cosmetic use is excluded from coverage in a typical pharmacy benefit.

W) 3. Use as Intranasal Irrigation Solution for Chronic Rhinosinusitis. Multiple small studies have assessed the use of fluticasone and mometasone nasal irrigations.[16,24] Results are not definitive and larger studies are needed to analyze differences between nasal sprays vs. irrigation.[24]

X)

Topical Hyaluronic Acid Derivatives

1. **Vaginal Atrophy.** Limited data are available with the use of hyaluronic acid derivatives in combination with other agents (e.g., vitamin E) for the treatment of vaginal atrophy;[10-14] however, to date, there is no evidence that products with hyaluronic acid have a greater benefit than nonhyaluronic acid lubricants or moisturizers.[15]

2. **Osteoarthritis (OA).** There are no published efficacy data available to support the use of non-FDA -approved, compounded formulations of hyaluronic acid and its derivatives for use in any OA or other pain-related conditions. Hyaluronic acid intra-articular injections (e.g., Euflexxa) are available as FDA-approved products for the treatment of OA of the knee.[9]

3. **Use in Any Other Medical Condition, Including, But Not Limited to Ophthalmic Procedures and Wound Care.** There are small studies showing some efficacy data surrounding the active hyaluronic acid ingredient[25], but no FDA-approved indications for topical hyaluronic use.

4. **Cosmetic Use (e.g., treatment of frown lines).** Cosmetic use is excluded from coverage in a typical pharmacy benefit.

Y) REFERENCES

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2. Lynch ME, Clark AJ, Sawynok J, et al. Topical 2% amitriptyline and 1% ketamine in neuropathic pain syndromes. *Anesthesiology*. 2005;103:140-146.
3. Mahoney JM, Vardaxis V, Moore JL, et al. Topical ketamine cream in the treatment of painful diabetic neuropathy. A randomized, placebo-controlled, double-blind initial study. *J Am Podiatr Med Assoc*. 2012;102:178-183.
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9. Clinical Pharmacology [database online]. Elsevier 2023. Available at http://www.clinicalpharmacology-ip.com/Default.aspx. Accessed on May 26, 2023. Search term: hyaluronic, fluticasone, mometasone.
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18. Diclofenac sodium 1% gel [consumer information]. Available at: www.voltarengel.com. Accessed on May 26, 2023..
19. Pennsaid® 2% topical solution [prescribing information]. Deerfield, IL: Horizon Therapeutics; January 2022.
20. Flector® patch [prescribing information]. Parsippany, NJ: IBSA Pharma; April 2021.
21. Diclofenac sodium ophthalmic® 0.1% solution [prescribing information]. Princeton, NJ: Sandoz; September 2021.
22. Flurbiprofen 0.03% ophthalmic solution [prescribing information]. Melville, NY: Amici Pharmaceuticals; December 2017.
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PRIOR AUTHORIZATION POLICY

POLICY: Contraceptives – Phexxi Prior Authorization Policy
- Phexxi™ (lactic acid, citric acid, and potassium bitartrate vaginal gel – Evofem)

REVIEW DATE: 05/17/2023

OVERVIEW

Phexxi is indicated for the **prevention of pregnancy** in females of reproductive potential for use as an on-demand method of contraception.[1] Limitation of Use: Phexxi is not effective for the prevention of pregnancy when administered after intercourse.

Phexxi contains lactic acid, citric acid, and potassium bitartrate; *in vitro* studies show that a pH lowering effect and sperm motility reduction contribute to the activity of the product in the vagina.[1] Phexxi has been previously known under multiple names, such as Amphora, Acidform, and was historically available as an over-the-counter (OTC) personal lubricant.[2] The recommended dose of Phexxi is one pre-filled applicator (5 grams) vaginally administered immediately before or up to one hour before each act of vaginal intercourse.[1] If more than one act of vaginal intercourse occurs within one hour, an additional dose must be used.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Phexxi. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Note: When compliance with the Affordable Care Act, HRSA Guidelines, and PHS Act section 2713 is required and the conditions for coverage listed under the Recommended Authorization Criteria are not met, approval is granted for the prevention of pregnancy if, according to the prescriber, other barrier methods of contraception would not be as medically appropriate for the patient as the requested drug.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Phexxi is recommended in those who meet the following criteria:

FDA-Approved Indication

5. **Prevention of Pregnancy.** Approve for 6 months if the patient has tried THREE other barrier methods of contraception (i.e., diaphragms, condoms, spermicides, or sponges).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Phexxi is not recommended in the following situations:

7. **As a Personal Lubricant.** The ingredients in Phexxi were previously available and marketed as an OTC personal lubricant.[2] Phexxi is currently only indicated for prevention of pregnancy.[1]

8. **Acute Episodes of Bacterial Vaginosis.** Low vaginal pH may provide a measure of protection against specific organisms.[2] In a pilot clinical study comparing Acidform gel with metronidazole gel for the treatment of symptomatic bacterial vaginosis, Acidform gel was significantly less effective.[3]

9. **For Protection Against Human Immunodeficiency Virus (HIV) or any other Sexually Transmitted Infections.** Per Phexxi labeling, it does not protect against HIV infection or other sexually transmitted infections.[1]

10. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

158. Phexxi™ vaginal gel [prescribing information]. San Diego, CA: Evofem; February 2022.
159. Nelson AL. An overview of properties of Amphora (Acidform) contraceptive vaginal gel. *Expert Opin Drug Saf.* 2018;17(9):935-943.
160. Simoes JA, Bahamondes LG, Camargo R, et al. A pilot clinical trial comparing an acid-buffering formulation (Acidform gel) with metronidazole gel for the treatment of symptomatic bacterial vaginosis. *Br J Clin Pharmacol.* 2006;61(2):211-17.

PRIOR AUTHORIZATION POLICY

POLICY: Coronavirus Disease – Evusheld Prior Authorization Policy
- Evusheld™ (tixagevimab intramuscular injection and cilgavimab intramuscular injection – AstraZeneca)

REVIEW DATE: 02/08/2023; selected revision 04/12/2023

OVERVIEW

On December 8, 2021 the FDA issued an Emergency Use Authorization (EUA) for Evusheld for pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19). Based on data showing that Evusheld is unlikely to be active against currently circulating variants of COVID-19, the FDA removed the EUA for Evusheld on January 26, 2023.

Evusheld, a combination product containing two severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein-directed attachment inhibitors, received EUA for the **pre-exposure prophylaxis of COVID-19** in patients ≥ 12 years of age and weighing ≥ 40 kg:[1]

- who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2; AND
- who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination; OR
- for whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a of severe adverse reactions (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).

Guidelines

The Infectious Disease Society of America (IDSA) and the National Institutes of Health (NIH) have developed treatment guidelines for the management of COVID-19 and each address the use of Evusheld.[2,3] The NIH recommends against the use of Evusheld for the pre-exposure prophylaxis of COVID-19.[2] In addition, the IDSA states that the benefits of prophylaxis with Evusheld no longer outweigh the small but known risks associated with its use.[3]

POLICY STATEMENT

Due to the lack of efficacy, **approval is not** recommended for Evusheld.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Evusheld is not recommended in the following situations:

11. **Coronavirus Disease 2019 (COVID-19), Pre-Exposure Prophylaxis.** Approval is not recommended. The FDA has removed the EUA for Evusheld due to the high combined frequency of non-susceptible

SARS-CoV-2 variants to Evusheld nationally.[4] According to the Centers for Disease Control and Prevention, the non-susceptible strains of SARS-CoV-2 are expected to account for > 90% of current infections. In addition, the NIH stated on January 30, 2023 that the prevalence of SARS-CoV-2 strains resistant to Evusheld is estimated to be > 97%.[5] The NIH now recommends against the use of Evusheld for pre-exposure prophylaxis of COVID-19.

12. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

161. Evusheld™ intramuscular injections [prescribing information]. Wilmington, DE: AstraZeneca; June 2022.
162. COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health. Available at: https://www.covid19treatmentguidelines.nih.gov/. Accessed on February 3, 2023.
163. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Disease Society of America Guidelines on the treatment and management of patients with COVID-19. January 20, 2023. Available at: https://www.idsociety.org/COVID19guidelines. Accessed February 3, 2023.
164. Food and Drug Administration. FDA announces Evusheld is not currently authorized for emergency use in the U.S. U.S. Food and Drug Administration Website. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-announces-evusheld-not-currently-authorized-emergency-use-us. Accessed on April 7, 2023.
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PRIOR AUTHORIZATION POLICY

POLICY: Coronavirus Disease – Veklury Prior Authorization Policy
- Veklury® (remdesivir intravenous infusion – Gilead)

REVIEW DATE: 12/13/2023

OVERVIEW

Veklury, a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleotide analog RNA polymerase inhibitor, is indicated for the treatment of **coronavirus disease 19 (COVID-19)** in patients ≥ 28 days of age and weighing ≥ 3 kg, who are:
- Hospitalized, or
- Not hospitalized and have mild-to-moderate COVID-19, and are at high risk of progression to severe COVID-19, including hospitalization or death.[1]

Guidelines

The Infectious Disease Society of America (IDSA) and the National Institutes of Health (NIH) have developed treatment guidelines for the management of COVID-19 and each address the use of Veklury.[2,3] Both the IDSA and NIH guidelines recommend Veklury for hospitalized patients with COVID-19 who require supplemental oxygen. For patients receiving supplemental oxygen, Veklury is recommended for 5 days of treatment. The IDSA and NIH recommend against the initiation of Veklury in patients receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). In patients who require mechanical ventilation or ECMO after initiating Veklury, a full 10 day course of Veklury should be administered. The IDSA and NIH also recommend 3 days of Veklury for non-hospitalized patients with mild-to-moderate COVID-19 who are at high risk of progression.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Veklury. All approvals are provided for the duration noted below. All reviews will be forwarded to the Medical Director for evaluation.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Veklury is recommended in those who meet the following criteria:

FDA-Approved Indication

6. Coronavirus Disease 2019 (COVID-19), Treatment. Approve for the duration noted if the patient meets the following (A, B, and C):
- **A)** Patient weight is ≥ 3 kilograms; AND
- **B)** Patient has tested positive for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); AND
- **C)** Patient meets one of the following (i or ii):
  - **i.** Approve for 10 days if the patient is being treated in a hospital; OR
  - **ii.** Approve for 3 days if the patient meets both of the following (a and b):

a) Patient is being treated in an outpatient setting; AND
b) Patient is at high risk of progression to severe COVID-19, according to the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Veklury is not recommended in the following situations:

13. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

166. Veklury intravenous infusion [prescribing information]. Foster City, CA: Gilead; August 2023.
167. COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health. November 02, 2023. Available at: https://www.covid19treatmentguidelines.nih.gov/. Accessed on December 11, 2023.
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PRIOR AUTHORIZATION POLICY

POLICY: Corticosteroids (Intraarticular) – Zilretta Prior Authorization Policy
- Zilretta® (triamcinolone acetonide extended-release intraarticular injection – Pacira)

REVIEW DATE: 05/03/2023

OVERVIEW

Zilretta, an **extended-release** synthetic corticosteroid, is indicated as an intraarticular injection for the management of **osteoarthritis pain of the knee**.[1]

Several other injectable corticosteroids (e.g., betamethasone sodium phosphate and betamethasone acetate, dexamethasone sodium phosphate, methylprednisolone acetate, and immediate-release triamcinolone acetonide) are indicated for intraarticular use for the management of osteoarthritic conditions.[2-5]

Dosing Information

Zilretta is administered as a single intraarticular injection that delivers 32 mg/5 mL.[1] The efficacy and safety of Zilretta for **repeat** administration have not been demonstrated.

Guidelines

Guidelines for the medical management of osteoarthritis of the hand, hip, and knee are available from the American College of Rheumatology (2019).[6] Multiple non-pharmacological modalities are recommended for knee osteoarthritis, including exercise, self-management programs, weight loss, Tai Chi, and use of assistive devices (i.e., bracing or a cane). Pharmacologic therapy for knee osteoarthritis consists of acetaminophen, oral and topical non-steroidal anti-inflammatory drugs, tramadol, intraarticular corticosteroid injections, duloxetine, and topical capsaicin. In the guidelines, no distinction is made between the available intraarticular corticosteroid products or between short-acting and long-acting products.

The American Academy of Orthopaedic Surgeons practice guideline for the management of osteoarthritis of the knee (2021) states intraarticular corticosteroids could provide **short-term** relief for patients with symptomatic osteoarthritis of the knee.[7] Additionally, extended-release intraarticular corticosteroids can be used over immediate-release to improve patient outcomes.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zilretta. All approvals are provided for the duration noted below.

Documentation: Documentation is required for use of Zilretta as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zilretta is recommended in those who meet the following criteria:

FDA-Approved Indication

7. **Osteoarthritis Pain of the Knee.** Approve for one injection per treated knee if the patient meets the following criteria (A, B, and C):
   - **A)** Diagnosis of the knee to be treated is confirmed by radiologic evidence of knee osteoarthritis; AND
     Note: Examples of radiologic evidence include diagnosis based on x-ray, magnetic resonance imaging, computed tomography scan, and ultrasound.
   - **B)** Patient has tried at least ONE intraarticular corticosteroid injection in the knee to be treated **[documentation required]**.
     Note: Examples of intraarticular corticosteroid injections include immediate-release triamcinolone acetonide, betamethasone sodium phosphate/betamethasone acetate, dexamethasone sodium phosphate, and methylprednisolone acetate.
   - **C)** Patient is not receiving re-treatment of knee(s) previously treated with Zilretta.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zilretta is not recommended in the following situations:

14. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

169. Zilretta® intraarticular injection [prescribing information]. San Diego, CA: Pacira Pharmaceuticals; March 2022.
170. Betamethasone sodium phosphate/betamethasone acetate injection [prescribing information]. Shirley, NY: American Regent; August 2019.
171. Dexamethasone sodium phosphate injection [prescribing information]. Lehi, UT: Civica; November 2019.
172. Methylprednisolone acetate injection [prescribing information]. Bridgewater, NJ: Amneal; November 2020.
173. Immediate-release triamcinolone acetonide injection [prescribing information]. Bridgewater, NJ: Amneal; December 2020.
174. Kolasinski SH, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Care Res.* 2019;72(2):149-162.
175. American Academy of Orthopaedic Surgeons Management of Osteoarthritis of the Knee (Non-Arthroplasty) Evidence-Based Clinical Practice Guideline. Published August 30, 2021. Available at: https://www.aaos.org/oak3cpg. Accessed on April 28, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Crysvita Prior Authorization Policy
- Crysvita® (burosumab-twza subcutaneous injection – Ultragenyx/Kyowa)

REVIEW DATE: 07/12/2023

OVERVIEW

Crysvita, a fibroblast growth factor 23 (FGF23) blocking antibody, is indicated for[1]:

- **Tumor-induced osteomalacia**, for treatment of FGF-related hypophosphatemia associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in patients ≥ 2 years of age.
- **X-linked hypophosphatemia** in patients ≥ 6 months of age.

Disease Overview

Tumor-Induced Osteomalacia

Tumor-induced osteomalacia is an extremely rare condition caused by tumors that produce the phosphaturic hormone FGF23, which causes renal phosphate wasting, and ultimately leads to hypophosphatemia, rickets, and osteomalacia. Tumor-induced osteomalacia is generally caused by small, slow-growing, benign phosphaturic mesenchymal tumors; complete resection of the tumor results in cure. However, in some cases, locating the tumor is not possible or the tumor may be inoperable. Patients usually present in adulthood with symptoms of fatigue, muscle weakness, and bone pain, which can lead to impaired mobility.[8] They may also experience decreased bone mineral density and frequent fractures. Current treatment of patients with inoperable or unidentifiable tumors has been phosphate supplementation and active vitamin D (e.g., calcitriol).

X-Linked Hypophosphatemia

X-linked hypophosphatemia is a condition that is believed to result from an inactivating genetic mutation in phosphate regulating endopeptidase on the X chromosome (PHEX).[2-5] This mutation leads to increased levels of FGF23, which increases phosphate excretion and abnormal vitamin D metabolism, ultimately leading to hypophosphatemic rickets.[2-4,6] Signs and symptoms of X-linked hypophosphatemia differ in pediatric patients who are still growing vs. adults whose epiphyseal plates have fused. In adults, symptoms include calcification of tendons, ligaments, and joint capsules; joint pain; impaired mobility; spontaneous dental abscesses; stress fractures; and sensorineural hearing loss. The X-linked hypophosphatemia diagnosis can be established in patients with a low serum phosphate concentration, a reduced tubular resorption of phosphate corrected for glomerular filtration rate (TmP/GFR), an inappropriate calcitriol level for the severity of hypophosphatemia, and/or by identification on molecular genetic testing of a hemizygous PHEX pathogenic variant in a male patient or a heterozygous PHEX pathogenic variant in a female patient. Genetic testing can provide a negative or positive confirmation in 70 to 90% of patients with suspected X-linked hypophosphatemia who lack a family .[5] If a genetic test is unavailable, an elevated FGF23 level can also support the diagnosis. However, FGF23 levels may be influenced by other factors, particularly phosphate and vitamin D therapy. FGF23 levels may be elevated in several other forms of hypophosphatemic rickets as well. Finally, the normal range of FGF23 varies according to the assay used.

Clinical Efficacy

Tumor-Induced Osteomalacia

Two studies evaluated the efficacy of Crysvita in patients with tumor-induced osteomalacia.[1,14,15] Eligible patients were adults with a confirmed diagnosis of FGF23-related hypophosphatemia produced by an underlying tumor that was not amenable to surgical excision or could not be located. In addition to low baseline serum phosphorus, patients were also required to have a low tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR) and a high FGF23 level. The vast majority of patients had previously received phosphate and active vitamin D therapy. Crysvita was found to increase the mean serum phosphorus level from baseline through Week 24 (Month 6) when levels stabilized.

X-Linked Hypophosphatemia

The efficacy of Crysvita for the treatment of X-linked hypophosphatemia was evaluated in several clinical trials in pediatric and adult patients with X-linked hypophosphatemia.[1] Eligible patients had baseline serum phosphorus levels less than the lower limit of normal for age.[1,9-11] Across the studies, Crysvita was found to increase mean serum phosphorus levels significantly from baseline. Radiographic improvements and healing of fractures/pseudofractures were also observed. Sustained efficacy has been demonstrated out to Week 96.[12,16] One additional study compared Crysvita with conventional therapy in patients 1 to 12 years of age with X-linked hypophosphatemia.[13] Following 64 weeks of therapy, patients receiving Crysvita had demonstrated a significantly greater improvement in the Radiographic Global Impression of Change global score compared with the conventional therapy group. In patients 5 to 12 years of age, sustained efficacy has been observed for up to 160 weeks, while there are extension data up to 168 weeks in adults.[17-19]

GUIDELINES

An expert panel has published Clinical Practice Recommendations for the Diagnosis and Management of X-linked hypophosphatemia (2019).[5] It is recommended that a clinical diagnosis of X-linked hypophosphatemia be confirmed by genetic analysis of the PHEX gene if feasible. In regard to treatment, oral phosphate and active vitamin D (e.g., calcitriol) are recommended for symptomatic adults with X-linked hypophosphatemia. Crysvita therapy should be considered for the treatment of adults with X-linked hypophosphatemia with the following features: persistent bone/joint pain due to X-linked hypophosphatemia and/or osteomalacia that limits daily activities; pseudofractures or osteomalacia-related fractures; and insufficient response or refractory to oral phosphate and active vitamin D. If patients experience complications related to oral phosphate and active vitamin D, Crysvita is recommended as well.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Crysvita. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Crysvita as well as the monitoring required for adverse events and long-term efficacy, approval requires Crysvita to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Crysvita is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Tumor-Induced Osteomalacia.** Approve Crysvita for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, vi, and vii):
     - **i.** Patient is ≥ 2 years of age; AND
     - **ii.** Patient has a mesenchymal tumor that cannot be curatively resected or identified/localized; AND
     - **iii.** Patient is currently exhibiting one or more signs or symptoms of tumor-induced osteomalacia, as determined by the prescriber; AND
       Note: Examples of signs and symptoms of tumor-induced osteomalacia include bone pain, impaired mobility, muscle weakness, and fatigue.
     - **iv.** Patient has had a baseline serum phosphorus level that was below the normal range for age; AND
       Note: "Baseline" is defined as prior to receiving any tumor-induced osteomalacia treatment, such as Crysvita, oral phosphate, or vitamin D therapy.
     - **v.** Patient has had a baseline tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR) that was below the normal range for age and gender; AND
       Note: "Baseline" is defined as prior to receiving any tumor-induced osteomalacia treatment, such as Crysvita, oral phosphate, or vitamin D therapy.
     - **vi.** Patient meets ONE of the following (a or b):
       - **1)** Patient has tried oral phosphate and calcitriol therapy; OR
       - **2)** Per the prescriber the patient has a contraindication to oral phosphate therapy, calcitriol therapy, or both; AND
     - **vii.** The medication is prescribed by or in consultation with an endocrinologist or nephrologist.
   - **B)** Patient is Currently Receiving Crysvita. Approve for 1 year if the patient is continuing to derive benefit from Crysvita as determined by the prescriber.
     Note: Examples of a response to Crysvita therapy are increased phosphorus levels, decreased symptoms of bone pain and/or muscle weakness, and increased mobility.

2. **X-Linked Hypophosphatemia.** Approve Crysvita for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient has had a baseline serum phosphorus level that was below the normal range for age; AND
       Note: "Baseline" is defined as prior to receiving any X-linked hypophosphatemia treatment, such as Crysvita, oral phosphate, or vitamin D therapy.
     - **ii.** Patient meets ONE of the following (a or b):
       - **a)** Patient has had a baseline tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR) that was below the normal range for age and gender; OR
         Note: "Baseline" is defined as prior to receiving any X-linked hypophosphatemia treatment, such as Crysvita, oral phosphate, or vitamin D therapy.
       - **b)** Patient has had a genetic test confirming the diagnosis of X-linked hypophosphatemia via identification of a PHEX mutation; AND
     - **iii.** If the patient is ≥ 18 years of age, the patient meets BOTH of the following (a and b):
       - **a)** Patient is currently exhibiting one or more signs or symptoms of X-linked hypophosphatemia, as determined by the prescriber; AND

Note: Examples of signs and symptoms of X-linked hypophosphatemia in patients ≥ 18 years of age include fractures/pseudofractures, bone and joint pain, muscle weakness, and impaired mobility.

b) Patient meets ONE of the following (1 or 2):

1) Patient has tried oral phosphate and calcitriol therapy; OR

2) Per the prescriber the patient has a contraindication to oral phosphate therapy, calcitriol therapy, or both; AND

iv. The medication is prescribed by or in consultation with an endocrinologist or nephrologist.

B) Patient is Currently Receiving Crysvita. Approve for 1 year if the patient is continuing to derive benefit from Crysvita as determined by the prescriber.

Note: Examples of a response to Crysvita therapy are increased phosphorus levels, radiographic improvement in deformities, healing of fractures/pseudofractures, reduction in the incidence of new fractures/pseudofractures.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Crysvita is not recommended in the following situations:

1. **Chronic Kidney Disease, Severe Renal Impairment or End Stage Renal Disease**. Crysvita is contraindicated in patients with severe renal impairment or end stage renal disease.[1] These patients often have abnormal mineral metabolism which may be associated with FGF23. However, Crysvita has not been studied for the treatment of patients with chronic kidney disease who have elevations of FGF23 impacting phosphate regulation.[1,9]

2. **Epidermal Nevus Syndrome**. More data are necessary to establish the efficacy and safety of Crysvita in patients with epidermal nevus syndrome. Patients with epidermal nevus syndrome were eligible to enroll in one of the Phase II tumor-induced osteomalacia studies of Crysvita.[15] However, no patients with epidermal nevus syndrome enrolled.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Cushing's – Isturisa Prior Authorization Policy
- Isturisa® (osilodrostat tablets – Recordati Rare Diseases)

REVIEW DATE: 06/14/2023

OVERVIEW

Isturisa, a cortisol synthesis inhibitor, is indicated for the treatment of **Cushing's disease** in adults for whom pituitary surgery is not an option or has not been curative.[1]

Disease Overview

Cushing's syndrome refers to the general state of excessive levels of cortisol (hypercortisolism) in the blood.[2,3] Hypercortisolism can occur for reasons that are either endogenous or exogenous in nature (e.g., Cushing's disease, cortisol-containing medications, adrenal gland tumor, certain cancers). Cushing's disease (hypercortisolism caused by pituitary adenomas) is the most common type of adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome. Treatment for Cushing's syndrome requires a multi-modal approach. The goals of treatment are normalization of cortisol excess, long-term disease control, avoidance of recurrence, and reversal of clinical features.[4]

Guidelines

The Endocrine Society published clinical practice guidelines (2015) for the treatment of Cushing's syndrome.[5] Isturisa is not addressed in the guidelines. First-line treatment involves resection of the tumor, unless surgery is not possible or is unlikely to meaningfully reduce excess glucocorticoid levels. In patients with ACTH-dependent Cushing's syndrome who underwent non-curative surgery or for whom surgery was not possible, the guidelines advocate several second-line therapies (e.g., repeat transsphenoidal surgery, radiotherapy, medical therapy, and bilateral adrenalectomy). For Cushing's disease, the guidelines recommend all medical therapies as second-line options after transsphenoidal surgery: steroidogenesis inhibitors (ketoconazole tablets, Metopirone® [metyrapone capsules], Lysodren® [mitotane tablets], etomidate injection) in patients either with or without radiotherapy/radiosurgery; pituitary-directed medical treatments (cabergoline tablets, Signifor® [pasireotide subcutaneous injection]) in patients who are not surgical candidates or who have persistent disease; and Korlym® (mifepristone tablets) in patients with diabetes or glucose intolerance who are not surgical candidates or who have persistent disease after transsphenoidal surgery.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Isturisa. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Isturisa as well as the monitoring required for adverse events and long-term efficacy, approval requires Isturisa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Isturisa is recommended in those who meet one of the following criteria:

FDA-Approved Indication

19. Cushing's Disease. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** According to the prescriber, the patient is not a candidate for surgery or surgery has not been curative; AND
  Note: For a patient with endogenous Cushing's syndrome awaiting surgery or therapeutic response after radiotherapy, see *Other Uses with Supportive Evidence*.
- **C)** Isturisa is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's disease.

Other Uses with Supportive Evidence

20. Endogenous Cushing's Syndrome. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** According to the prescriber, the patient is not a candidate for surgery or surgery has not been curative; AND
  Note: For a patient with endogenous Cushing's syndrome awaiting surgery or therapeutic response after radiotherapy, see *Other Uses with Supportive Evidence*.
- **C)** Patient meets ONE of the following criteria (i or ii):
  - **i.** Patient has tried one of ketoconazole tablets, Korlym (mifepristone tablets), Metopirone (metyrapone capsules), Lysodren (mitotane tablets), Signifor (pasireotide subcutaneous injection), or Signifor LAR (pasireotide intramuscular injection) for the treatment of endogenous Cushing's syndrome; OR
  - **ii.** Patient is currently receiving Isturisa; AND
- **D)** Isturisa is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of endogenous Cushing's syndrome.

3. Endogenous Cushing's Syndrome – Patient Awaiting Surgery. Approve for 4 months if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Isturisa is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of endogenous Cushing's syndrome.

4. Endogenous Cushing's Syndrome – Patient Awaiting Therapeutic Response after Radiotherapy. Approve for 4 months if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Isturisa is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of endogenous Cushing's syndrome.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Isturisa is not recommended in the following situations:

15. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Cushing's – Korlym Prior Authorization Policy
- Korlym® (mifepristone 300 mg tablets – Corcept)

REVIEW DATE: 06/14/2023

OVERVIEW

Korlym, a cortisol receptor blocker, is indicated to control hyperglycemia secondary to hypercortisolism in adults with **endogenous Cushing's syndrome** who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.[1]

Korlym should not be used for the treatment of type 2 diabetes mellitus unrelated to endogenous Cushing's syndrome.[1]

Disease Overview

Cushing's syndrome refers to the general state of excessive levels of cortisol (hypercortisolism) in the blood.[2,3] Hypercortisolism can occur for reasons that are either endogenous or exogenous in nature (e.g., Cushing's disease, cortisol-containing medications, adrenal gland tumor, certain cancers). Cushing's disease (hypercortisolism caused by pituitary adenomas) is the most common type of adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome. Treatment for Cushing's syndrome requires a multi-modal approach. The goals of treatment are normalization of cortisol excess, long-term disease control, avoidance of recurrence, and reversal of clinical features.[4]

Guidelines

The Endocrine Society published clinical practice guidelines (2015) for the treatment of Cushing's syndrome.[5] First-line treatment involves resection of the tumor, unless surgery is not possible or is unlikely to meaningfully reduce excess glucocorticoid levels. In patients with ACTH-dependent Cushing's syndrome who underwent non-curative surgery or for whom surgery was not possible, the guidelines advocate several second-line therapies (e.g., repeat transsphenoidal surgery, radiotherapy, medical therapy, and bilateral adrenalectomy). For Cushing's disease, the guidelines recommend all medical therapies as second-line options after transsphenoidal surgery: steroidogenesis inhibitors (ketoconazole tablets, Metopirone® [metyrapone capsules], Lysodren® [mitotane tablets], etomidate injection) in patients either with or without radiotherapy/radiosurgery; pituitary-directed medical treatments (cabergoline tablets, Signifor® [pasireotide subcutaneous injection]) in patients who are not surgical candidates or who have persistent disease; and Korlym® (mifepristone tablets) in patients with diabetes or glucose intolerance who are not surgical candidates or who have persistent disease after transsphenoidal surgery.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Korlym. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Korlym as well as the monitoring required for adverse events and long-term efficacy, approval requires Korlym to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Korlym is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. **Endogenous Cushing's Syndrome.** Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Korlym is being used to control hyperglycemia secondary to hypercortisolism in patients who have type 2 diabetes mellitus or glucose intolerance; AND
   - **C)** According to the prescriber, the patient is not a candidate for surgery or surgery has not been curative; AND
     Note: For a patient with endogenous Cushing's syndrome awaiting surgery or therapeutic response after radiotherapy, see *Other Uses with Supportive Evidence*.
   - **D)** Patient meets ONE of the following (i or ii):
     - **i.** Patient has tried one of ketoconazole tablets, Metopirone (metyrapone capsules), Lysodren (mitotane tablets), Signifor (pasireotide subcutaneous injection), or Signifor LAR (pasireotide intramuscular injection) for the treatment of endogenous Cushing's syndrome; OR
     - **ii.** Patient is currently receiving Korlym; AND
   - **E)** Korlym is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome.

Other Uses with Supportive Evidence

2. **Endogenous Cushing's Syndrome – Patient Awaiting Surgery.** Approve for 4 months if the patient meets the following criteria (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Korylm is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of endogenous Cushing's syndrome.

3. **Endogenous Cushing's Syndrome – Patient Awaiting Response after Radiotherapy.** Approve for 4 months if the patient meets the following criteria (A and B):
   - A) Patient is ≥ 18 years of age; AND
   - B) Korlym is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of endogenous Cushing's syndrome.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Korlym is not recommended in the following situations:

16. **Type 2 Diabetes Not Associated with Endogenous Cushing's Syndrome.** Korlym should not be used for the treatment of type 2 diabetes unrelated to endogenous Cushing's syndrome.[1]

17. **Psychotic Features of Psychotic Depression.** Mifepristone has been used to treat the psychotic features of psychotic depression. Individual trials have demonstrated variable efficacy results.[6,7] In some of the studies comparing mifepristone with placebo, various statistically significant improvements in psychiatric symptoms have been noted with mifepristone relative to placebo;

however, the methodology and statistical analyses of some studies have been questioned. Data are inconclusive.

18. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Cushing's – Recorlev Prior Authorization Policy
- Recorlev® (levoketoconazole tablets – Xeris)

REVIEW DATE: 01/18/2023

OVERVIEW

Recorlev, a cortisol synthesis inhibitor, is indicated for the treatment of endogenous hypercortisolemia in adults with **Cushing's syndrome** for whom surgery is not an option or has not been curative. Recorlev was approved through the 505(b)(2) pathway and as such relied upon existing safety and efficacy information for ketoconazole tablets to support approval. Recorlev contains levoketoconazole as the active ingredient. Levoketoconazole is the 2S, 4R-enantiomer derived from racemic ketoconazole.

Cushing's syndrome refers to the general state of excessive levels of cortisol (hypercortisolism) in the blood.[2,3] Hypercortisolism can occur for reasons that are either endogenous or exogenous in nature (e.g., Cushing's disease, cortisol-containing medications, adrenal gland tumor, certain cancers). Cushing's disease (hypercortisolism caused by pituitary adenomas) is the most common type of adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome. Treatment for Cushing's syndrome requires a multi-modal approach. The goals of treatment are normalization of cortisol excess, long-term disease control, avoidance of recurrence, and reversal of clinical features.[4]

Guidelines

The Endocrine Society published clinical practice guidelines (2015) for the treatment of Cushing's syndrome.[5] Recorlev is not addressed in the guidelines. First-line treatment involves resection of the tumor, unless surgery is not possible or is unlikely to meaningfully reduce excess glucocorticoid levels. In patients with ACTH-dependent Cushing's syndrome who underwent non-curative surgery or for whom surgery was not possible, the guidelines advocate several second-line therapies (e.g., repeat transsphenoidal surgery, radiotherapy, medical therapy, and bilateral adrenalectomy). For Cushing's disease, the guidelines recommend all medical therapies as second-line options after transsphenoidal surgery: steroidogenesis inhibitors (ketoconazole, Metopirone® [metyrapone capsules], Lysodren® [mitotane tablets], etomidate) in patients either with or without radiotherapy/radiosurgery; pituitary-directed medical treatments (cabergoline, Signifor® [pasireotide subcutaneous injection]) in patients who are not surgical candidates or who have persistent disease; and Korlym® (mifepristone tablets) in patients with diabetes or glucose intolerance who are not surgical candidates or who have persistent disease after transsphenoidal surgery.

A 2021 guideline update does recognize Recorlev as an investigational drug for the treatment of Cushing's syndrome, but do not give recommendations for therapy placement within existing medications.[6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Recorlev. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Recorlev as well as the monitoring required for adverse events and long-term efficacy, approval requires Recorlev to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Recorlev is recommended in those who meet one of the following criteria:

FDA-Approved Indication

21. Endogenous Cushing's Syndrome. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
- **E)** Patient is ≥ 18 years of age; AND
- **F)** Patient has hypercortisolemia; AND
- **G)** According to the prescriber, the patient is not a candidate for surgery or surgery has not been curative; AND
  Note: For a patient with endogenous Cushing's syndrome awaiting surgery or therapeutic response after radiotherapy, see *Other Uses with Supportive Evidence.*
- **H)** Patient has tried ketoconazole tablets; AND
- **I)** The medication is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of endogenous Cushing's syndrome.

Other Uses with Supportive Evidence

22. Endogenous Cushing's Syndrome – Patient Awaiting Surgery. Approve for 4 months if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has hypercortisolemia; AND
- **C)** Patient has tried ketoconazole tablets; AND
- **D)** The medication is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of endogenous Cushing's syndrome.

23. Endogenous Cushing's Syndrome – Patient Awaiting Therapeutic Response After Radiotherapy. Approve for 4 months if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has hypercortisolemia; AND
- **C)** Patient has tried ketoconazole tablets; AND
- **D)** The medication is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of endogenous Cushing's syndrome.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Recorlev is not recommended in the following situations:

19. Fungal Infections. Recorlev is not approved for the treatment of fungal infections.[1]

20. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Cushing's – Signifor Prior Authorization Policy
- Signifor™ (pasireotide subcutaneous injection – Novartis)

REVIEW DATE: 06/14/2023

OVERVIEW

Signifor, a somatostatin analog, is indicated for the treatment of **Cushing's disease** in adults for whom pituitary surgery is not an option or has not been curative.[1]

Disease Overview

Cushing's syndrome refers to the general state of excessive levels of cortisol (hypercortisolism) in the blood.[2,3] Hypercortisolism can occur for reasons that are either endogenous or exogenous in nature (e.g., Cushing's disease, cortisol-containing medications, adrenal gland tumor, certain cancers). Cushing's disease (hypercortisolism caused by pituitary adenomas) is the most common type of adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome. Treatment for Cushing's syndrome requires a multi-modal approach. The goals of treatment are normalization of cortisol excess, long-term disease control, avoidance of recurrence, and reversal of clinical features.[4]

Guidelines

The Endocrine Society published clinical practice guidelines (2015) for the treatment of Cushing's syndrome.[5] First-line treatment involves resection of the tumor, unless surgery is not possible or is unlikely to meaningfully reduce excess glucocorticoid levels. In patients with ACTH-dependent Cushing's syndrome who underwent non-curative surgery or for whom surgery was not possible, the guidelines advocate several second-line therapies (e.g., repeat transsphenoidal surgery, radiotherapy, medical therapy, and bilateral adrenalectomy). For Cushing's disease, the guidelines recommend medical therapies as second-line options after transsphenoidal surgery: steroidogenesis inhibitors (ketoconazole tablets, Metopirone® [metyrapone capsules], Lysodren® [mitotane tablets], etomidate injection) in patients either with or without radiotherapy/radiosurgery; pituitary-directed medical treatments (cabergoline tablets, Signifor) in patients who are not surgical candidates or who have persistent disease; and Korlym® (mifepristone tablets) in patients with diabetes or glucose intolerance who are not surgical candidates or who have persistent disease after transsphenoidal surgery.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Signifor. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Signifor as well as the monitoring required for adverse events and long-term efficacy, approval requires Signifor to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Signifor is recommended in those who meet one of the following criteria:

FDA-Approved Indication

24. Cushing's Disease. Approve for the duration noted below if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets the following criteria (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. According to the prescriber, the patient is not a candidate for surgery or surgery has not been curative; AND

Note: For patients with endogenous Cushing's syndrome awaiting surgery or therapeutic response after radiotherapy, see *Other Uses with Supportive Evidence*.

iii. Signifor is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome.

B) Patient is Currently Receiving Signifor/Signifor LAR. Approve for 1 year if the patient has had a response, as determined by the prescriber; and patient is continuing therapy to maintain response.

Other Uses with Supportive Evidence

2. Endogenous Cushing's Syndrome – Patient Awaiting Surgery. Approve for 4 months if the patient meets the following criteria (A and B):

A) Patient is ≥ 18 years of age; AND

B) Signifor is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome.

3. Endogenous Cushing's Syndrome – Patient Awaiting Therapeutic Response After Radiotherapy. Approve for 4 months if the patient meets the following criteria (A and B):

A) Patient is ≥ 18 years of age; AND

B) Signifor is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Signifor is not recommended in the following situations:

21. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

208. Signifor® subcutaneous injection [prescribing information]. Lebanon, NJ: Recordati Rare Diseases; March 2020.

209. Sharma ST, Nieman LK, Feelders RA. Cushing's syndrome: epidemiology and developments in disease management. *Clin Epidemiol*. 2015;7:281–293.

210. Tritos NA, Biller BM. Advances in medical therapies for Cushing's syndrome. *Discov Med*. 2012;13(69):171-179.

211. Biller BMK, Grossman AB, Stewart PM, et al. Treatment of adrenocorticotropin-dependent Cushing's syndrome: A consensus statement. *J Clin Endocrinol Metab*. 2008;93:2454-2462.

212. Nieman LK, Biller BM, Findling JW. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2015;100(8):2807-2831.

PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Bronchitol Prior Authorization Policy
- Bronchitol® (mannitol oral inhalation powder – Pharmaxis/Chiesi)

REVIEW DATE: 02/08/2023

OVERVIEW

Bronchitol, a sugar alcohol, is indicated as add-on maintenance therapy to improve pulmonary function in patients ≥ 18 years of age with **cystic fibrosis** (CF).[1]

Safety

Bronchitol can cause bronchospasm, which can be severe in susceptible patients.[1] Therefore, Bronchitol is contraindicated in individuals who fail to pass the Bronchitol Tolerance Test. Prior to prescribing Bronchitol, the Bronchitol Tolerance Test must be administered and performed under the supervision of a healthcare practitioner who is able to manage acute bronchospasm, to identify patients who are suitable candidates for Bronchitol maintenance therapy. For patients who have passed the Bronchitol Tolerance Test, the recommended dosage of Bronchitol is 400 mg twice a day by oral inhalation (the contents of 10 capsules administered individually) via the inhaler. A short-acting bronchodilator should be administered by oral inhalation, 5 to 15 minutes before every dose of Bronchitol. Bronchitol should be taken once in the morning and once in the evening, with the later dose taken at least 2 to 3 hours before bedtime.

Guidelines

Bronchitol is not addressed in US guidelines for CF. Guidelines from the CF Foundation (2013) in the US strongly recommend chronic use of Pulmozyme® (dornase alfa inhalation solution) in patients ≥ 6 years of age with moderate to severe disease to improve lung function, quality of life, and reduce exacerbations. Pulmozyme is also recommended for chronic use in patients ≥ 6 years of age with asymptomatic or mild disease to improve lung function and reduce exacerbations. Chronic use of hypertonic saline is also recommended in individuals with CF who are ≥ 6 years of age to improve lung function and quality of life and reduce exacerbations.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Bronchitol. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Bronchitol as well as the monitoring required for adverse events and long-term efficacy, approval requires Bronchitol to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Bronchitol is recommended in those who meet the following criteria:

FDA-Approved Indication

8. Cystic Fibrosis. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has tried hypertonic saline; AND
- **C)** Patient has passed the Bronchitol Tolerance Test; AND
- **D)** Patient will pre-medicate with a short-acting bronchodilator; AND
- **E)** The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Bronchitol is not recommended in the following situations:

22. Concomitant Use with Hypertonic Saline. Bronchitol has not been studied in combination with hypertonic saline.[3-5]

23. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

213. Bronchitol® oral inhalation powder [prescribing information]. Frenchs Forest NSW, Australia/Cary, NC: Pharmaxis/Chiesi; October 2020.
214. Mogayzel PJ, Naureckas ET, Robinson KA, et al. Pulmonary clinical practice guidelines committee. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2013;187(7):680-689.
215. Flume P, Amelina E, Daines CL, et al. Efficacy and safety of inhaled dry-powder mannitol in adults with cystic fibrosis: An international, randomized controlled study. *J Cyst Fibr*. 2020;30(6):1003-1009.
216. Bilton D, Robinson P, cooper P, et al; for the CF301 Study Investigators. Inhaled dry powder mannitol in cystic fibrosis: an efficacy and safety study. *Eur Respir J*. 2011;38:1071-1080.
217. Aitken ML, Bellon G, De Boeck K, et al; for the CF302 Investigators. Long-term inhaled dry powder mannitol in cystic fibrosis. An international randomized study. *Am J Respir Crit Care*. 2012;185(6): 645-652.

PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Kalydeco Prior Authorization Policy
- Kalydeco® (ivacaftor tablets and oral granules – Vertex)

REVIEW DATE: 02/08/2023; selected revision 05/10/2023

OVERVIEW

Kalydeco, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, is indicated for the treatment of **cystic fibrosis (CF)** in patients ≥ 1 months of age who have one mutation in the CFTR gene that is responsive to Kalydeco potentiation based on clinical and/or *in vitro* assay data.[1]

In patients with unknown genotype, a FDA-cleared CF mutation test should be used to detect the presence of the CFTR mutation followed by verification with bidirectional sequencing when recommended by the mutation test instructions for use.[1] Kalydeco is not effective in patients with CF who are homozygous for the F508del mutation in the CFTR. A patient must have at least one CFTR mutation responsive to Kalydeco to be indicated. Table 1 lists mutations that are responsive to Kalydeco based on 1) a positive clinical response and/or 2) *in vitro* data in Fischer rat thyroid cells indicating that Kalydeco increases chloride transport to ≥ 10% over baseline (% of normal).

Table 1. List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Kalydeco.[1]
CFTR – Cystic fibrosis transmembrane regulator.

Guidelines

Guidelines from the CF Foundation (2018) provide guidance on the use of CFTR therapy in patients with CF. Symdeko (tezacaftor/ivacaftor and ivacaftor tablets) and Trikafta (elexacaftor/tezacaftor/ivacaftor tablets; ivacaftor tablets, co-packaged and elexacaftor/tezacaftor/ivacaftor oral granules; ivacaftor oral granules) are not addressed and neither is the lower pediatric age indication for Kalydeco.[2] For adults ≥ 6 years of age with CF due to a gating mutation other than G551D or R117H (e.g., G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, or G1249D), the guidelines make a conditional recommendation for treatment with Kalydeco. For those with the R117H mutation, the guideline panel made a conditional recommendation for treatment with Kalydeco for adults ≥ 18 years of age and for children 6 to 17 years of age with a percent predicted forced expiratory volume in 1 second (ppFEV1) < 90%. For individuals with R117H mutation, the guidelines recommend against treatment with Kalydeco for children 12 to 17 years of age with a (ppFEV1) > 90% and in children < 6 years of age.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Kalydeco. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kalydeco as well as the monitoring required for adverse events and efficacy, approval requires Kalydeco to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kalydeco is recommended in those who meet the following criteria:

FDA-Approved Indication

9. Cystic Fibrosis. Approve for 1 year in patients who meet the following criteria (A, B, and C):
- **A)** Patient is ≥ 1 month of age; AND
- **B)** Patient has at least ONE of the following mutations in the cystic fibrosis transmembrane conductance regulator gene: E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, A455E, D579G, S945L, S977F, F1052V, K1060T, A1067T, G1069R, R1070Q, R1070W, F1074L, D1152H, D1270N, G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D, 2789+5G—>A, 3272-26A—>G, 3849+10kbC—>T, 711+3A—>G, E831X, R117H, A120T, A234D, A349V, D192G, D924N, E882K, F311L, F311delF508C, F508C;S1251N, G178E, G194R, G314E, G576A, G970D, G1249R, H939R, H1375P, I148T, I175V, I807M, I1027T, I1139V, L320V, L967S, L997F, L1480P, M152V, M9521, M952T, Q237E, Q237H, Q359R, Q1291R, R75Q, R117G, R117L, R117P, R170H, R347L, R553Q, R668C, R792G, R933G, R1162L, R1283M, S589N, S737F, S1159F, S1159P, T338I, T1053I, V232D, V562I, V754M, V1293G, W1282R, Y1014C, or Y1032C; AND
- **C)** The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kalydeco is not recommended in the following situations:

1. Cystic Fibrosis (CF), Patients who are Homozygous for the phe508del (F508del) Mutation in the Cystic Fibrosis Transmembrane Regulator Gene. Efficacy results from a double-blind, placebo controlled trial in patients with CF who were homozygous for the phe508del mutation in the CFTR gene showed no statistically significant difference in forced expiratory volume in 1 second (FEV_1) over 16 weeks of Kalydeco treatment compared with placebo.[1] In a Phase II trial in patients homozygous for the F508del (n = 112), Kalydeco did not result in an improvement in FEV_1 relative to placebo.[3]

63. Cystic Fibrosis (CF), Patients with Unknown Cystic Fibrosis Transmembrane Regulator Gene Mutation. An FDA-cleared CF mutation test should be used to detect the presence of the cystic fibrosis transmembrane regulator mutation prior to use of Kalydeco.[1]

64. Combination Therapy with Orkambi, Symdeko, or Trikafta. Orkambi, Symdeko, and Trikafta contain ivacaftor, the active agent in Kalydeco and therefore are not indicated in combination with Kalydeco.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

194. Kalydeco® tablets and oral granules [prescribing information]. Cambridge, MA: Vertex; May 2023.
195. Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Foundation Pulmonary Guidelines: Use of cystic fibrosis transmembrane conductance regulator modulator therapy in patients with cystic fibrosis. *Ann Am Thorac Soc.* 2018;15(3):271-280.
196. Flume PA, Liou TG, Borowitz DS, et al; VX08-770-104 Study Group. Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. *Chest.* 2012;142(3):718-724.

PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Orkambi Prior Authorization Policy
- Orkambi® (lumacaftor/ivacaftor tablets and oral granules – Vertex)

REVIEW DATE: 07/05/2023

OVERVIEW

Orkambi, a combination of lumacaftor and ivacaftor, is indicated for the treatment of **cystic fibrosis** in patients ≥ 1 year of age who are homozygous for the F508del mutation in the cystic fibrosis transmembrane regulator (CFTR) gene.[1]

If the patient's genotype is unknown, an FDA-cleared cystic fibrosis mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene. The efficacy and safety of Orkambi have not been established in patients with cystic fibrosis other than those homozygous for the F508del mutation. Orkambi contains a unique chemical entity, lumacaftor, which is a CFTR corrector that increases trafficking of F508del CFTR to the cell surface, and ivacaftor (the same active ingredient contained in Kalydeco® [ivacaftor tablets and oral granules]), a CFTR potentiator that enhances chloride transport of CFTR on the cell surface. The F508del mutation in CFTR causes cystic fibrosis by limiting the amount of CFTR protein that reaches the epithelial cell surface.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Orkambi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Orkambi as well as the monitoring required for adverse events and long-term efficacy, approval requires Orkambi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Orkambi is recommended in those who meet the following criteria:

FDA-Approved Indication

10. Cystic Fibrosis, Homozygous for the F508del (Phe508del) Mutation in the Cystic Fibrosis Transmembrane Regulator (CFTR) Gene. Approve for 1 year if the patient meets all of the following (A, B, and C):
- **A)** Patient is ≥ 1 year of age; AND
- **B)** Patient is homozygous for the F508del (Phe508del) mutation in the CFTR gene (meaning the patient has two copies of the F508del [Phe508del] mutation); AND
- **C)** The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Orkambi is not recommended in the following situations:

24. **Cystic Fibrosis, Heterozygous for the F508del (Phe508del) Mutation in the CFTR Gene.** Orkambi is not indicated for patients with only one copy of the F508del mutation in the CFTR gene.[1]

25. **Combination Therapy with Kalydeco (ivacaftor tablets and oral granules), Symdeko (tezacaftor/ivacaftor; ivacaftor tablets, co-packaged), or Trikafta (elexacaftor/tezacaftor/ivacaftor tablets; ivacaftor tablets, co-packaged).** Orkambi contains ivacaftor, the active agent in Kalydeco and therefore is not indicated in combination with Kalydeco. Symdeko and Trikafta contain ivacaftor and are therefore not indicated in combination with Orkambi.

26. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

218. Orkambi® tablets and oral granules [prescribing information]. Cambridge, MA: Vertex; September 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Pulmozyme Prior Authorization Policy
- Pulmozyme® (dornase alfa inhalation solution – Genentech/Roche)

REVIEW DATE: 05/17/2023

OVERVIEW
Pulmozyme, a recombinant human deoxyribonuclease I, is indicated in conjunction with standard therapies for the management of patients with **cystic fibrosis** to improve pulmonary function.[1]
9.
10. Guidelines
According to Patient Registry data compiled by the Cystic Fibrosis Foundation (2021), Pulmozyme is used by the vast majority of patients with cystic fibrosis.[2] Guidelines from the Cystic Fibrosis Foundation (2007, updated in 2013) address the chronic use of medications for management of lung health in cystic fibrosis patients 6 years of age and older.[3,4] These guidelines recommend Pulmozyme use for cystic fibrosis patients regardless of disease severity to improve lung function and reduce exacerbations. Separate guidelines have addressed Pulmozyme use in younger patients.[5,6] Although efficacy data are lacking in patients under 5 years of age, safety and tolerability have been established in patients as young as 3 months.[1,6] Cystic Fibrosis Foundation guidelines for infants under 2 years of age (2009) and children between 2 and 5 years of age (2016) support Pulmozyme use in these populations based on individual circumstances.[5,6]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Pulmozyme. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Pulmozyme as well as the monitoring required for adverse events and long-term efficacy, approval requires Pulmozyme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Pulmozyme is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Cystic Fibrosis.** Approve for 1 year if the medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Pulmozyme is not recommended in the following situations:

1. **Asthma.** Mucus hypersecretion may be mediated by a variety of causes, including inflammation, irritation, stimulation, or mucus-producing tumors.[7] However, efficacy of Pulmozyme is not established for conditions other than cystic fibrosis. In a pilot study of patients with severe acute asthma (n = 50), there was no significant difference in forced expiratory volume in 1 second (FEV_1) with Pulmozyme use vs. placebo.[8]

2. **Bronchiectasis, Idiopathic.** A multicenter, double-blind, randomized, placebo-controlled 24-week trial (n = 349) examined the effect of Pulmozyme vs. placebo in patients with idiopathic bronchiectasis (i.e., bronchiectasis not related to cystic fibrosis).[9] Patients in the Pulmozyme arm experienced worsened lung function and more frequent pulmonary exacerbations vs. placebo. The authors concluded that Pulmozyme should not be used in this population.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

197. Pulmozyme® inhalation solution [prescribing information]. South San Francisco, CA: Genentech/Roche; July 2021.
198. Cystic Fibrosis Foundation. Patient Registry: 2021 Annual Data Report. Available at: https://www.cff.org/medical-professionals/patient-registry. Accessed on May 9, 2023.
199. Flume PA, O'Sullivan BP, Robinson KA, et al. Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health. *Am J Respir Crit Care Med*. 2007;176:957-969.
200. Mogayzel PJ Jr, Naureckas ET, Robinson KA, et al, Pulmonary Clinical Practice Guidelines Committee. Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health. *Am J Respir Crit Care Med*. 2013;187(7):680-689.
201. Borowitz D, Robinson KA, Rosenfeld M, et al, Cystic Fibrosis Foundation. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. *J Pediatr*. 2009;155(6 Suppl):S73-93.
202. Lahiri T, Hempstead SE, Brady C, et al. Clinical practice guidelines from the Cystic Fibrosis Foundation for preschoolers with cystic fibrosis. *Pediatrics*. 2016;137(4): e20151784.
203. Rubin BK. Aerosol medications for treatment of mucus clearance disorders. *Respiratory Care*. 2015;60(6):825-832.
204. Silverman RA, Foley F, Dalipi R, et al. The use of rhDNase in severely ill, non-intubated adult asthmatics refractory to bronchodilators: a pilot study. *Respir Med*. 2012; 106(8):1096-1102.
205. O'Donnell AE, Barker AF, Ilowite JS, Fick RB. Treatment of idiopathic bronchiectasis with aerosolized recombinant human DNase I. rhDNase Study Group. *Chest*. 1998;113(5):1329-1334.

PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Symdeko Prior Authorization Policy
- Symdeko® (tezacaftor/ivacaftor and ivacaftor tablets – Vertex)

REVIEW DATE: 02/08/2023

OVERVIEW

Symdeko is indicated for the treatment of patients ≥ 6 years of age with **cystic fibrosis** (CF) who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence.[1]

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use. Table 1 lists responsive CFTR mutations based on: 1) a clinical forced expiratory volume in 1 second (FEV_1) response and/or 2) *in vitro* data in Fischer rat thyroid cells, indicating that tezacaftor/ivacaftor increases chloride transport to ≥ 10% of untreated normal over baseline. CFTR gene mutations that are not responsive to Kalydeco® (ivacaftor granule or tablet) alone are not expected to respond to Symdeko except for F508del homozygotes.

Table 1. List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Symdeko.[1]
Table 1 (continued). List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Symdeko.[1]
CFTR – Cystic fibrosis transmembrane regulator; * A patient must have two copies of the F508del mutation or at least one copy of a responsive mutation presented in Table 1 to be indicated.

Guidelines

Guidelines from the CF Foundation (2018) provide guidance on the use of CFTR therapy in patients with CF; Symdeko is not addressed.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Symdeko. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Symdeko as well as the monitoring required for adverse events and efficacy, approval requires Symdeko to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Symdeko is recommended in those who meet the following criteria:

FDA-Approved Indications

21. Cystic Fibrosis. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 6 years of age; AND
- **B)** Patient meets ONE of the following conditions (i or ii):

i. Patient has at least one of the following mutations in the cystic fibrosis transmembrane conductance regulator gene: E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, A455E, D579G, 711+3A → G, S945L, S977F, F1052V, E831X, K1060T, A1067T, R1070W, F1074L, D1152H, D1270N, 2789+5G → A, 3272-26A → G, 3849 + 10kbC → T, 546insCTA, A120T, A234D, A349V, A554E, A1006E, D192G, D443Y, D443Y;G57A;R668C, D614G, D836Y, D924N, D979V, I618T, I807M, I980K, I1027T, I1139V, I1269N, I1366N, L15P, L320V, R170H, R258G, R334L, R334Q, R347L, R347P, R352W, R553Q, R668C, R751L, V1293G, E60K, E92K, E116K, E403D, E558V, E822K, F191V, F311del, F311L, F508C, F508C;S1251N, F575Y, L346P, L967S, L997F, L1324P, L1335P, L1480P, M152V, M265R, M9521, R1066H, R1070Q, R1162L, R1283M, R1283S, S549N, S549R, S589N, S737F, S912L, F1016S, F1099L, G126D, G178E, G178R, G194R, G194V, G314E, G551D, G551S, G576A, G576A;R668C, M952T, P5L, P205S, Q98R, Q237E, Q237H, Q359R, Q1291R, R31L, S1251N, S1255P, T338I, T1036N, T1053I, V201M, V232D, V562I, V754M, V1153E, G622D, G970D, G1069R, G1244E, G1249R, G1349D, H939R, H1054D, H1375P, I148T, I175V, I336K, I601F, R74Q, R74W;D1270N, R74W;V201M, R74W;V201M;D1270N, R75Q, R117G, R117H, R117L, R117P, W1282R, Y109N, Y161S, Y1014C, Y1032C, R792G, R933G, S1159F, S1159P, or V1240G; OR

ii. Patient has two copies of the F508del mutation; AND

C) The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Symdeko is not recommended in the following situations:

1. **Cystic Fibrosis (CF), Patients with Unknown Cystic Fibrosis Transmembrane Regulator (CFTR) Gene Mutation.** An FDA-cleared CF mutation test should be used to detect the presence of the CFTR mutation prior to use of Symdeko.[1]

65. **Combination Therapy with Orkambi, Kalydeco, or Trikafta.** Symdeko contains ivacaftor, the active agent in Kalydeco and part of Orkambi and Trikafta. Symdeko also contains tezacaftor, part of Trikafta. Symdeko is not indicated in combination with Kalydeco, Orkambi, or Trikafta.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

206. Symdeko® tablets [prescribing information]. Cambridge, MA: Vertex; December 2020.
207. Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Foundation Pulmonary Guidelines: Use of cystic fibrosis transmembrane conductance regulator modulator therapy in patients with cystic fibrosis. *Ann Am Thorac Soc.* 2018;15(3):271-280.

PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Trikafta Prior Authorization Policy
- Trikafta® (elexacaftor/tezacaftor/ivacaftor tablets; ivacaftor tablets, co-packaged and elexacaftor/tezacaftor/ivacaftor oral granules; ivacaftor oral granules – Vertex)

REVIEW DATE: 05/03/2023

OVERVIEW

Trikafta is a combination of ivacaftor, a cystic fibrosis transmembrane regulator (CFTR) potentiator, tezacaftor, and elexacaftor. It is indicated for the **treatment of cystic fibrosis (CF)** in patients ≥ 2 years of age who:
- Have at least one F508del mutation in the CFTR gene; OR
- Have a mutation in the CFTR gene that is responsive to Trikafta based on in vitro data.[1]

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one F508del mutation. Table 1 lists responsive CFTR mutations based on *in vitro* data in Fischer Rat Thyroid cells.

Table 1. List of CFTR Gene Mutations that are Responsive to Trikafta.[1]
CFTR – Cystic Fibrosis Transmembrane Regulator.

Guidelines

Guidelines from the CF Foundation (2018) provide guidance on the use of CFTR therapy in patients with CF; Trikafta is not addressed.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Trikafta. All approvals are provided for 1 year unless otherwise noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Trikafta as well as the monitoring required for adverse events and long-term efficacy, approval requires Trikafta to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Trikafta is recommended in those who meet the following criteria:

FDA-Approved Indication

11. Cystic Fibrosis (CF). Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 2 years of age; AND
- **B)** Patient has at least one copy of one of the following mutations in the cystic fibrosis conductance regulator gene: F508del, 3141del9, E822K, G1069R, L967S, R117L, S912L, 546insCTA, F191V, G1244E, L997F, R117P, S945L, A46D, F311del, G1249R, L1077P, R170H, S977F, A120T, F311L, G1349D, L1324P, R258G, S1159F, A234D, F508C, H139R, L1335P, R334L, S1159P, A349V, F508C;S1251N, H199Y, L1480P, R334Q, S1251N, A455E, H939R, M152V, R347H, S1255P, A554E, F575Y, H1054D, M265R, R347L, T338I, A1006E, F1016S, H1085P, M952I,

R347P, T1036N, A1067T, F1052V, H1085R, M952T, R352Q, T1053I, D110E, F1074L, H1375P, M1101K, R352W, V201M, D110H, F1099L, I148T, P5L, R553Q, V232D, D192G, G27R, I175V, P67L, R668C, V456A, D443Y, G85E, I336K, P205S, R751L, V456F, D443Y;G576A;R668C, G126D, I502T, P574H, R792G, V562I, D579G, G178E, I601F, Q98R, R933G, V754M, D614G, G178R, I618T, Q237E, R1066H, V1153E, D836Y, G194R, I807M, Q237H, R1070Q, V1240G, D924N, G194V, I980K, Q359R, R1070W, V1293G, D979V, G314E, I1027T, Q1291R, R1162L, W361R, D1152H, G463V, I1139V, R31L, R1283M, W1098C, D1270N, G480C, I1269N, R74Q, R1283S, W1282R, E56K, G551D, I1366N, R74W, S13F, Y109N, E60K, G551S, K1060T, R74W;D1270N, S341P, Y161D, E92K, G576A, L15P, R74W;V201M, S364P, Y161S, E116K, G576A;R668C, L165S, R74W;V201M;D1270N, S492F, Y563N, E193K, G622D, L206W, R75Q, S549N, Y1014C, E403D, G628R, L320V, R117C, S549R, Y1032C, E474K, G970D, L346P, R117G, S589N, E588V, G1061R, L453S, R117H, or S737F; AND

C) The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of CF.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Trikafta is not recommended in the following situations:

27. **Cystic Fibrosis (CF), Patient with Unknown Cystic Fibrosis Transmembrane Regulator (CFTR) Gene Mutation.** An FDA-cleared CF mutation test should be used to detect the presence of the CFTR mutation prior to use of Trikafta.[1]

28. **Combination Therapy with Orkambi, Kalydeco, or Symdeko.** Trikafta contains ivacaftor which is a component of Orkambi (lumacaftor/ivacaftor tablets and oral granules), Kalydeco (tablets and oral granules), and Symdeko (tezacaftor/ivacaftor tablets; ivacaftor tablets). Tezacaftor, another component of Trikafta is also contained in Symdeko.

29. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

219. Trikafta® tablets [prescribing information]. Cambridge, MA: Vertex; April 2023.
220. Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Foundation Pulmonary Guidelines: Use of cystic fibrosis transmembrane conductance regulator modulator therapy in patients with cystic fibrosis. *Ann Am Thorac Soc.* 2018;15(3):271-280.

PRIOR AUTHORIZATION POLICY

POLICY: Dermatology – Gene Therapy – Vyjuvek Prior Authorization Policy
- Vyjuvek™ (beremagene geperpavec-svdt biological suspension – Krystal Biotech)

REVIEW DATE: 06/28/2023; selected revision 09/13/2023, 09/27/2023, and 10/11/2023

OVERVIEW

Vyjuvek, a herpes-simplex virus type-1 (HSV-1) vector-based gene therapy, is indicated for the treatment of wounds in patients ≥ 6 months of age with **dystrophic epidermolysis bullosa** (DEB) with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene.[1]

Vyjuvek is a live, replication defective HSV-1-based vector that has been genetically modified to express the human type VII collagen (COL7) protein.[1] Mutation(s) in the COL7A1 gene result in reduced or absent levels of biologically active COL7 in patients with DEB. COL7 protein is a crucial component of anchoring fibrils that are essential for maintaining skin integrity. Application of Vyjuvek to wounds results in transcription of the encoded human COL7A1 and production and secretion of COL7 by the cell in its mature form. The COL7 molecules form anchoring fibrils that hold the epidermis and dermis together.

DEB usually presents at birth and is divided into two major types depending on the pattern of inheritance: recessive DEB (RDEB) and dominant DEB (DDEB).[6] All subtypes of DEB are caused by mutations in the gene coding COL7A1 leading to extreme skin fragility.[4,6] The hallmark of DEB is scarring of blisters, both on the skin and on other mucosal surfaces.[4]

Clinical Efficacy

GEM-3, a Phase III, double-blind, placebo-controlled, intrapatient randomized, pivotal study, assigned patients with DEB to treat two similarly sized wounds; one with Vyjuvek and one with placebo for 26 weeks (N = 31).[2] Eligible patients were ≥ 6 months of age presenting with a clinical diagnosis of DEB, characterized by blistering, wounds, and scarring and confirmed by genetic testing including COL7A1. The appearance of the wounds was to be clean with adequate granulation tissue, excellent vascularization, and to not appear infected. Patients receiving immunotherapy, chemotherapy, or other investigational products were not included. In addition, wound sites with current evidence or a history of squamous-cell carcinoma or active infection were excluded as sites for Vyjuvek (or placebo) application. Vyjuvek or placebo was applied only to open wounds. Wounds were evaluated weekly to determine continued application of Vyjuvek or placebo. If a healed wound reopened, application was resumed; if the wound remained closed, application was omitted. All but one patient had the recessive DEB genotype. At Month 6, significantly more Vyjuvek- vs. placebo-treated wounds were completely healed (67% vs. 22%, respectively; P = 0.002) [primary endpoint]. Similar results were observed at Month 3 favoring Vyjuvek vs. placebo for complete wound healing (71% vs. 20%, respectively; P < 0.001). Durability (complete wound healing at both Months 3 and 6) was seen in 50% vs. 7% of Vyjuvek- vs. placebo-treated wounds, respectively (difference 43%; 95% confidence interval: 23%, 63%). One patient had a chronic secondary wound of the back measuring > 100 cm^2 that had been open for > 10 years. Following Vyjuvek treatment, the patient was able to resume activities of daily living, including showering, which had not previously been possible due to the open nature of the wound.

Guidelines

Vyjuvek is not addressed in available guidelines. According to a position statement by the **European Reference Network for Rare Skin Diseases** (2021), wound care is the cornerstone of treatment for patients with DEB.[5] Careful and complete skin and wound assessment should be undertaken regularly, at least every 6 months. The healing rate of chronic wounds should be closely monitored, by checking wound edges.

The diagnosis of DEB is based on a combination of clinical features, family , and laboratory findings.[5] Laboratory techniques include immunofluorescence mapping, transmission electron microscopy, and molecular genetic testing. Whenever possible, laboratory diagnosis should be performed in a specialized DEB center. Genetic testing is the gold standard for the diagnosis of DEB, since it provides a definitive diagnosis and classification of the major DEB type and in many cases the subtype.

An **international consensus best practice guideline** on skin and wound care in epidermolysis bullosa (EB) [2017] notes that EB is a lifelong disease that requires specialist intervention and consideration to minimize complications and improve quality of life.[6] Management should take place in a specialized center by a multi-disciplinary team, ideally. Definitive diagnosis is most commonly made from analysis of a skin biopsy using positive immunofluorescence, antigenic mapping, and transmission electron microscopy. These key diagnostic tools help confirm diagnosis and indicate the particular subtype of EB. Due to the rarity of expertise and facilities, diagnosis is generally made using immunofluorescence and antigen mapping. Some laboratories are moving towards molecular diagnosis from exome sequencing of a panel of known skin fragility genes. Experienced clinicians can often make a provisional diagnosis on clinical observations, but a definitive diagnosis will always be required.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vyjuvek. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vyjuvek as well as the monitoring required for adverse events and long-term efficacy, approval requires Vyjuvek to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Vyjuvek as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vyjuvek is recommended in those who meet the following criteria:

FDA-Approved Indication

12. Dystrophic Epidermolysis Bullosa. Approve for the duration outlined below if the patient meets ONE of the following (A or B):

- Note: For new wound(s) the patient is directed to Initial Therapy criteria. If the patient is continuing to treat the same wound(s) the patient is directed to criteria for Patient Currently Receiving Vyjuvek on Previously Treated Wound(s).

A) Initial Therapy: Approve for 6 months if the patient meets the following (i, ii, iii, and iv):

i. Patient is ≥ 6 months of age; AND

ii. The diagnosis is confirmed by genetic testing showing a pathogenic mutation in the collagen type VII alpha 1 chain (COL7A1) gene **[documentation required]**; AND

iii. Patient meets ALL of the following (a, b, and c):

a) Patient has at least one clinical feature of dystrophic epidermolysis bullosa **[documentation required]**; AND

- Note: Examples of clinical features of dystrophic epidermolysis bullosa include but are not limited to blistering, wounds, and scarring.

b) Patient has one or more open wound(s) that will be treated (i.e., "target wound[s]); AND

c) Target wound(s) meet the following, according to the prescriber [(1), (2), and (3)]:

(1) Target wound(s) is clean in appearance and does not appear to be infected; AND

(2) Target wound(s) has adequate granulation tissue and vascularization; AND

(3) Squamous cell carcinoma has been ruled out for the target wound(s); AND

iv. The medication is prescribed by or in consultation with a dermatologist or wound care specialist with expertise in the management of dystrophic epidermolysis bullosa.

B) Patient is Currently Receiving Vyjuvek on **Previously Treated Wound(s)**: Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

- Note: If the patient is treating a new wound(s) not previously treated with Vyjuvek or a reopened recurrent wound(s), then refer to Initial Therapy criteria above.

i. According to the prescriber, the target wound(s) remains open; AND

ii. According to the prescriber, the target wound(s) has decreased in size from baseline; AND

iii. The medication is prescribed by or in consultation with a dermatologist or wound care specialist with expertise in the management of dystrophic epidermolysis bullosa.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vyjuvek is not recommended in the following situations:

30. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

34. Vyjuvek™ biological suspension [prescribing information]. Pittsburgh, PA: Krystal Biotech; May 2023.
35. Guide SV, Gonzalez ME, Bagci IS, et al. Trial of beremagene geperavec (B-VEC) for dystrophic epidermolysis bullosa. *N Engl J Med*. 2022;387(24):2211-2219.
36. Payne AS. Topical gene therapy for epidermolysis bullosa. *N Engl J Med*. 2022;387(24):2281-2284.
37. Has C, Bauer JW, Bolling MC et al. Consensus and reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. *Br J Dermatol*. 2020;183:614-627.
38. Has C, El Hachem M, Buckova H, et al. Practical management of epidermolysis bullosa: consensus clinical position statement from the European Reference Network for Rare Skin Diseases. *J Eur Acad Derm Venereol*. 2021;35:2349-2360.
39. Denyer J, Pillay E, Clapham J. Best practice guidelines for skin and wound care in epidermolysis bullosa. An International Consensus. *Wounds International*. 2017. Available at: https://af13d689-15eb-4199-8733-e91a7bb8ae3f.usrfiles.com/ugd/af13d6_01ed147ab87e49c584c20a917c47f19f.pdf. Accessed on: June 26, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Dermatology – Hyftor Prior Authorization Policy
- Hyftor™ (sirolimus 0.2% topical gel – Nobelpharma)

REVIEW DATE: 05/24/2023

OVERVIEW

Hyftor, a topical mammalian target of rapamycin inhibitor immunosuppressant, is indicated for the treatment of **facial angiofibroma associated with tuberous sclerosis** in patients ≥ 6 years of age.[1]

Disease Overview

Tuberous sclerosis complex is an autosomal dominant genetic disorder caused by mutations in two genes, tuberous sclerosis 1 and tuberous sclerosis 2.[2-4] The incidence rate is approximately one in 6,000 to 10,000 births. It is characterized by non-cancerous (benign) tumors that grow in the brain, as well as in other vital organs such as the kidneys, heart, eyes, lungs, and skin. It can also impact the central nervous system causing seizures, impaired intellectual development, autism, and behavioral issues. The disease has great variability but can occur when patients are very young (around 1 year of age). Most patients (up to 80%) experience various skin conditions due to the disease such as angiofibromas, hypomelanotic macules, and cephalic plaques. Angiofibromas in the face usually appear in young children and gradually proliferate thereafter. This manifestation can be serious as well as disfiguring.

Clinical Efficacy

The efficacy of Hyftor for its approved use was evaluated in one Phase III, randomized, double-blind, vehicle-controlled, multicenter pivotal study conducted in Japan involving 62 patients who were 6 years of age and older.[1,2] The trial enrolled patients with tuberous sclerosis complex who had three or more facial angiofibromas that were at least 2 mm in diameter with redness present in each. Patients also had a definitive diagnosis of tuberous sclerosis complex. Use of Hyftor reduced the lesion size and redness of the facial angiofibromas after 12 weeks of use compared with vehicle.[1,2] The assessment at 4 weeks after discontinuation of Hyftor suggests that continuation of therapy is required for benefit.[2] It is recommended that if symptoms do not improve within 12 weeks of Hyftor treatment, the need for continuing Hyftor should be reevalauted.[1]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Hyftor. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Hyftor as well as the monitoring required for adverse events and long-term efficacy, approval requires Hyftor to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Hyftor is recommended in those who meet the following criteria:

FDA-Approved Indication

13. Facial Angiofibroma Associated with Tuberous Sclerosis. Approve for the duration noted below if the patient meets one of the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following criteria (i, ii, iii, and iv):

- **i.** Patient is ≥ 6 years of age; AND
- **ii.** Patient has a definitive diagnosis of tuberous sclerosis complex by meeting one of the following criteria (a or b):
  - **a)** There is identification of a pathogenic variant in the tuberous sclerosis complex 1 (*TSC1*) gene or tuberous sclerosis complex 2 (*TSC2*) gene by genetic testing; OR
  - **b)** According to the prescriber, clinical diagnostic criteria suggest a definitive diagnosis of tuberous sclerosis complex by meeting either two major features or one major feature with two minor features; AND

    Note: Major feature criteria involve angiofibroma (three or more) or fibrous cephalic plaque; angiomyolipomas (two or more); cardiac rhabdomyoma; hypomelanotic macules (three or more; at least 5 mm in diameter); lymphangiomyomatosis; multiple cortical tubers and/or radial migration lines; multiple retinal hamartomas; Shagreen patch; subependymal giant cell astrocytoma; subependymal nodule (two or more); or ungula fibromas (two or more). Minor feature criteria involve "confetti" skin lesions; dental enamel pits (three or more); intraoral fibromas (two or more); multiple renal cysts; nonrenal hamartomas; retinal achromic patch; and sclerotic bone lesions.
- **iii.** Patient has three or more facial angiofibromas that are at least 2 mm in diameter with redness in each; AND
- **iv.** The medication is prescribed by or in consultation with a dermatologist or a physician who specializes in the management of patients with tuberous sclerosis complex; OR

B) Patient Currently Receiving Hyftor. Approve for 1 year if the patient meets the following criteria (i, ii, iii, and iv):

- **i.** Patient is ≥ 6 years of age; AND
- **ii.** Patient has a definitive diagnosis of tuberous sclerosis complex by meeting one of the following criteria (a or b):
  - **a)** There is identification of a pathogenic variant in the tuberous sclerosis complex 1 (*TSC1*) gene or tuberous sclerosis complex 2 (*TSC2*) gene by genetic testing; OR
  - **b)** According to the prescriber, clinical diagnostic criteria suggest a definitive diagnosis of tuberous sclerosis complex by meeting either two major features or one major feature with two minor features; AND

    Note: Major feature criteria involve angiofibroma (three or more) or fibrous cephalic plaque; angiomyolipomas (two or more); cardiac rhabdomyoma; hypomelanotic macules (three or more; at least 5 mm in diameter); lymphangiomyomatosis; multiple cortical tubers and/or radial migration lines; multiple retinal hamartomas; Shagreen patch; subependymal giant cell astrocytoma; subependymal nodule (two or more); or ungula fibromas (two or more). Minor feature criteria involve "confetti" skin lesions; dental enamel pits (three or more); intraoral fibromas (two or more); multiple renal cysts; nonrenal hamartomas; retinal achromic patch; and sclerotic bone lesions.
- **iii.** Patient has responded to Hyftor as evidenced by a reduction in the size and/or redness of the facial angiofibromas, as determined by the prescriber; AND
- **iv.** The medication is prescribed by or in consultation with a dermatologist or a physician who specializes in the management of patients with tuberous sclerosis complex.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Hyftor is not recommended in the following situations:

31. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

221. Hyftor™ 0.2% topical gel [prescribing information]. Bethesda, MD: Nobelpharma; March 2022.
222. Wataya-Kaneda M, Ohno Y, Fujita Y, et al. Sirolimus gel treatment vs. placebo for facial angiofibromas in patients with tuberous sclerosis complex. A randomized clinical trial. *JAMA Dermatol*. 2018;154(7):781-788.
223. Krueger DA, Northrup H, on behalf of the International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 international tuberous sclerosis complex consensus conference. *Pediatric Neurol*. 2013;49(4):255-265.
224. Northrup H, Aronow ME, Bebin EM, et al, on behalf of the International Tuberous Sclerosis Complex Consensus Group. Updated international tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations. *Pediatric Neurol*. 2021;123:50-66.

PRIOR AUTHORIZATION POLICY

POLICY: Dermatology – Opzelura Prior Authorization Policy
- Opzelura® (ruxolitinib 1.5% cream – Incyte)

REVIEW DATE: 08/16/2023

OVERVIEW

Opzelura, a Janus kinase (JAK) inhibitor, is indicated for the following uses:[1]

- **Atopic dermatitis**, for the topical short-term and non-continuous treatment of mild to moderate disease in patients ≥ 12 years of age whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.
- **Nonsegmental vitiligo**, for the topical treatment of patients ≥ 12 years of age.

Limitation of Use: Use of Opzelura in combination with therapeutic biologics, other JAK inhibitors, or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.

For atopic dermatitis, Opzelura is applied twice daily to affected areas of up to 20% body surface area (BSA). Patients should stop using Opzelura when signs and symptoms of atopic dermatitis (e.g., itch, rash, and redness) resolve. If signs and symptoms do not improve within 8 weeks, patients should be re-examined by their healthcare provider.

For vitiligo, Opzelura is applied twice daily to affected areas of up to 10% BSA.[1] Patients may require more than 24 weeks of treatment to achieve a satisfactory response. If the patient does not find the repigmentation meaningful after 24 weeks of therapy, the patient should be re-evaluated by their healthcare provider.

Clinical Efficacy

Atopic Dermatitis

Two pivotal Opzelura studies enrolled patients ≥ 12 years of age with a diagnosis of atopic dermatitis present for ≥ 2 years, affecting 3% to 20% of their BSA.[1,2] Patients were also required to have an Investigator's Global Assessment (IGA) score of 2 or 3. While prior treatment was not a requirement for study enrollment, 90% of patients had received prior therapies for atopic dermatitis, including low-, medium-, and high-potency topical corticosteroids (49.6%, 42.4%, and 32.7% of patients, respectively), as well as topical calcineurin inhibitors (21.5% of patients). At Week 8, Opzelura cream was found to be more effective in achieving IGA treatment success, defined as an IGA score of 0 (clear) or 1 (almost clear) with a ≥ 2-grade improvement from baseline.[3] A third, non-pivotal, Phase II trial of Opzelura cream in a similar patient population included a triamcinolone acetonide 0.1% cream comparator arm.[4] At Week 4, Opzelura 1.5% cream produced greater improvement in the Eczema Area and Severity Index score from baseline; however, the treatment difference vs. triamcinolone was not statistically significant.

Vitiligo

One Phase III Opzelura study enrolled patients ≥ 12 years of age with a diagnosis of non-segmental vitiligo and depigmented areas covering ≤ 10% of their BSA.[5] While prior treatment was not a requirement for study enrollment, 61% of patients had received prior topical therapies for vitiligo, including topical corticosteroids and topical calcineurin inhibitors. Efficacy was evaluated at Week 24.

Guidelines

Atopic Dermatitis Guidelines

In general, The American Academy of Dermatology Guidelines of Care for the Management of Atopic Dermatitis (2014) recommends moisturizers/emollients as first-line therapy, followed by topical corticosteroids, when appropriate.[6] Topical calcineurin inhibitors (i.e., tacrolimus 0.03% and 0.1% ointment [Protopic®, generic] and pimecrolimus 1% cream [Elidel®, generic]) are recommended for the treatment of atopic dermatitis, particularly when use of topical corticosteroids is not appropriate due to safety concerns (e.g., young infants, treatment of sensitive areas such as the face, eyelids, or genitalia). Opzelura is recommended for the treatment of patients with mild to moderate atopic dermatitis. However, Opzelura should not be used on more than 20% of the patient's BSA to avoid potential adverse events.

Vitiligo Guidelines

Guidelines from the British Association of Dermatologists for the management of vitiligo (2021) do not address Opzelura.[7] A potent or very potent topical corticosteroid therapy should be offered to patients. As an alternative to topical corticosteroids, topical tacrolimus, a calcineurin inhibitor, may be considered. These therapies may also be used in combination as part of an intermittent therapy regimen. In general, efficacy of a topical corticosteroid or topical calcineurin inhibitor may not be evident for 8 to 12 weeks.[8]

Safety

Opzelura carries a Boxed Warning regarding the risk of serious infections, mortality, malignancy and lymphoproliferative disorders, major adverse cardiac events, and thrombosis.[1] Other Warnings and Precautions include thrombocytopenia, anemia, neutropenia, and lipid elevations. Based on these risks, critical evaluation and monitoring of certain patients is recommended in the Opzelura prescribing information.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Opzelura cream. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Opzelura cream as well as the monitoring required for adverse events and long-term efficacy, approval requires Opzelura cream to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Opzelura cream is recommended in those who meet one of the following criteria:

FDA-Approved Indications

14. Atopic Dermatitis. Approve for 8 weeks if the patient meets all of the following (A, B, C, D, E, and F):
- **A)** Patient is ≥ 12 years of age; AND
- **B)** Patient has mild to moderate atopic dermatitis, according to the prescriber; AND
- **C)** Patient has atopic dermatitis involvement estimated to affect ≤ 20% of the body surface area; AND
- **D)** Patient meets ONE of the following (i or ii):
  - **i.** Patient meets ALL of the following (a, b, and c):
    - **a)** Patient has tried at least one medium-, medium-high, high-, and/or super-high-potency prescription topical corticosteroid; AND

Note: Concomitant use of a topical corticosteroid with a topical calcineurin inhibitor would meet the requirement.

b) This topical corticosteroid was applied daily for at least 28 consecutive days; AND

c) Inadequate efficacy was demonstrated with this topical corticosteroid therapy, according to the prescriber; OR

ii. Patient is treating atopic dermatitis affecting one of the following areas: face, eyes/eyelids, skin folds, and/or genitalia; AND

E) Patients meets ALL of the following (i, ii, and iii):

i. Patient has tried at least one topical calcineurin inhibitor; AND
Note: Examples of topical calcineurin inhibitors include tacrolimus ointment (Protopic, generic) and pimecrolimus cream (Elidel, generic). Concomitant use of a topical calcineurin inhibitor with a topical corticosteroid would meet the requirement.

ii. This topical calcineurin inhibitor was applied daily for at least 28 consecutive days; AND

iii. Inadequate efficacy was demonstrated with this topical calcineurin inhibitor, according to the prescriber; AND

F) The medication is prescribed by or in consultation with an allergist, immunologist, or dermatologist.

15. Vitiligo. Approve for 6 months if the patient meets all of the following (A, B, C, D, E, and F):

A) Patient is ≥ 12 years of age; AND

B) Patient has nonsegmental vitiligo; AND

C) Patient has vitiligo involvement estimated to affect ≤ 10% of the body surface area; AND

D) Patient meets ONE of the following (i or ii):

i. Patient meets ALL of the following (a, b, and c):

a) Patient has tried at least one high-, and/or super-high-potency prescription topical corticosteroid; AND
Note: Concomitant use of a topical corticosteroid with a topical calcineurin inhibitor would meet the requirement.

b) The duration of this topical corticosteroid therapy was at least 12 weeks; AND
Note: Intermittent or continuous use of a topical corticosteroid for at least 12 weeks would meet the requirement.

c) Inadequate efficacy was demonstrated with this topical corticosteroid therapy, according to the prescriber; OR

ii. Patient is treating vitiligo affecting one of the following areas: face, eyes/eyelids, skin folds, and/or genitalia; AND

E) Patients meets ALL of the following (i, ii, and iii):

i. Patient has tried at least one topical calcineurin inhibitor; AND
Note: Examples of topical calcineurin inhibitors include tacrolimus ointment (Protopic, generic) and pimecrolimus cream (Elidel, generic). Concomitant use of a topical calcineurin inhibitor with a topical corticosteroid would meet the requirement.

ii. This topical calcineurin inhibitor was applied daily for at least 12 weeks; AND

iii. Inadequate efficacy was demonstrated with this topical calcineurin inhibitor, according to the prescriber; AND

The medication is prescribed by or in consultation with a dermatologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Opzelura cream is not recommended in the following situations:

32. **Concurrent Use with a Biologic or with other JAK inhibitors.** Use of Opzelura in combination with therapeutic biologics or other JAK inhibitors is not recommended (see Appendix for examples).[1] Use of biologics or other JAK inhibitors was prohibited during the Opzelura pivotal studies.[2] There are no data evaluating combination use of Opzelura with these therapies; therefore, safety and efficacy of these combinations are unknown.

33. **Concurrent use with Other Potent Immunosuppressants** (e.g., azathioprine, cyclosporine). Use of Opzelura in combination with potent immunosuppressants is not recommended.[1] Use of systemic immunosuppressants was prohibited during the Opzelura pivotal studies.[2] There are no data evaluating combination of Opzelura with these therapies; therefore, safety and efficacy of these combinations are unknown.

34. **Alopecia.** Opzelura is not indicated for the treatment of alopecia.[1] A Phase II study involving patients with alopecia areata did not find any significant improvement in hair regrowth with Opzelura 1.5% cream compared with vehicle.[9] Additional data are needed to establish the efficacy and safety of Opzelura in patients with alopecia.

35. **Plaque Psoriasis.** Opzelura is not indicated for the treatment of plaque psoriasis.[1] There are very limited Phase II data regarding the use of Opzelura in patients with plaque psoriasis.[10,11] Additional data are needed to establish the efficacy and safety of Opzelura in patients with plaque psoriasis.

36. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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APPENDIX

Table 1. Examples of Other Therapeutic Biologics and Other JAK Inhibitors.

JAK – Janus kinase; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous; IL – Interleukin; PDE4 – Phosphodiesterase 4; TYK2 – Tyrosine kinase 2; IgE – Immunoglobulin E; TSLP – Thymic stromal lymphopoietin.

PRIOR AUTHORIZATION POLICY

POLICY: Desmopressin Products – Nocdurna Prior Authorization Policy
- Nocdurna® (desmopressin acetate sublingual tablets [27.7 mcg and 55.3 mcg] – Ferring)

REVIEW DATE: 11/15/2023

OVERVIEW

Nocdurna, a vasopressin analog, is indicated for the treatment of **nocturia due to nocturnal polyuria** in adults who awaken at least two times per night to void.[1] Before initiating therapy, it is recommended that the diagnosis of nocturnal polyuria has been confirmed with a 24-hour urine collection.

Disease Overview

Nocturnal polyuria is defined as nocturnal urine volume exceeding 33% of the total 24-hour urine volume in patients ≥ 65 years of age or exceeding 20% of 24-hour urine volume in younger patients.[2] Nocturnal polyuria may improve via lifestyle and behavior modifications, which should be implemented prior to pharmacotherapy.[3] Such modifications include minimizing fluid intake before bed (particularly caffeine and alcohol), restriction of total fluid consumption, emptying the bladder before bed, increasing exercise and fitness levels, earlier dosing of medications such as diuretics, and elevating the legs above heart level for a few hours before going to bed (for patients with peripheral edema).

Safety

Nocdurna has a Boxed Warning regarding hyponatremia.[1] Use of Nocdurna is contraindicated in patients at increased risk of severe hyponatremia such as patients with excessive fluid intake, illness that may cause fluid or electrolyte imbalances, and in patients using loop diuretics or systemic or inhaled glucocorticoids. It is recommended to check serum sodium concentrations prior to initiating or resuming Nocdurna and throughout treatment. If hyponatremia occurs, Nocdurna may need to be temporarily or permanently discontinued. Nocdurna is contraindicated in patients with hyponatremia or among those with a history of hyponatremia.[1] Also, patients with polydipsia should not use Nocdurna. Do not administer Nocdurna concomitantly with loop diuretics or with systemic or inhaled glucocorticoids. Patients with renal impairment with an estimated glomerular filtration rate below 50 mL/min/1.73 m^2 should not use Nocdurna. Those with known or suspected syndrome of inappropriate antidiuretic hormone secretion should not use Nocdurna. Do not utilize Nocdurna during illnesses that may cause fluid or electrolyte imbalance, such as gastroenteritis, salt-wasting nephropathies, or systemic infection. Nocdurna is contraindicated in patients with heart failure or among those with uncontrolled hypertension because the fluid retention in these conditions increases the risk of worsening the underlying condition. Also, Nocdurna is not recommended in patients at risk for increased intracranial pressure or those with a of urinary retention. Trials involving Nocdurna have not included pediatric patients.

Guidelines

A consensus statement on the diagnosis and treatment of nocturia was published by the International Continence Society in 2019.[2] There was consensus that fluid restriction should be advised for all desmopressin-treated patients. Newer desmopressin formulations, including Nocdurna and Noctiva® (desmopressin acetate nasal spray), are generally regarded as low-dose desmopressin. Low-dose formulations are appropriate in the absence of contraindications to desmopressin therapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Nocdurna. All approvals are provided for the duration noted below. Due to the specialized skills required for evaluation and diagnosis of patients treated with Nocdurna, as well as the monitoring required for adverse events and long-term efficacy, approval requires Nocdurna to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nocdurna is recommended in those who meet the following criteria:

FDA-Approved Indication

25. Nocturia due to Nocturnal Polyuria. Approve for 1 year if the patient meets all of the following (A, B, C, D, E, F, and G):

G) Patient is ≥ 18 years of age; AND

H) The diagnosis of nocturnal polyuria has been confirmed with a 24-hour urine collection before treatment initiation AND the patient meets one of the following (i or ii):

- **i.** The nocturnal urine volume exceeds 20% of the total 24-hour urine volume if the patient is < 65 years of age; OR
- **ii.** The nocturnal urine volume exceeds 33% of the total 24-hour urine volume if the patient is ≥ 65 years of age; AND

I) Prior to desmopressin therapy, patient awakens at least two times per night to void; AND

J) Patient has serum sodium concentrations within the normal range (135 to 145 mmol/L); AND

K) Prescriber has verified that the patient does not have the following conditions/circumstances in which use of Nocdurna is not recommended (i, ii, iii, iv, v, or vi):

- **i.** Currently receiving loop diuretics (e.g., furosemide, torsemide, bumetanide); OR
- **ii.** Currently receiving systemic or inhaled glucocorticoids; OR
- **iii.** Renal impairment with an estimated glomerular filtration rate < 50 mL/min/1.73 m^2; OR
- **iv.** Heart failure; OR
- **v.** Polydipsia; OR
- **vi.** Known or suspected syndrome of inappropriate antidiuretic hormone secretion; AND

L) Patient has tried non-pharmacologic techniques or lifestyle interventions to manage the nocturia; AND

Note: Examples of non-pharmacologic techniques for nocturia include nighttime fluid restriction, avoidance of caffeine and alcohol, earlier timing of medications, leg elevation, or use of compression stockings.

M) The medication is prescribed by or in consultation with a nephrologist, urologist, geriatrician, or endocrinologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nocdurna is not recommended in the following situations:

66. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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91. Weiss JP, Everaert K. Management of nocturia and nocturnal polyuria. *Urology*. 2019;133S:24-33.

PRIOR AUTHORIZATION WITH STEP THERAPY POLICY

POLICY: Desmopressin Products – Noctiva Prior Authorization with Step Therapy Policy

- Noctiva™ (desmopressin acetate nasal spray [0.83 mcg/0.1 mL and 1.66 mcg/0.1 mL] – Avadel)

REVIEW DATE: 11/15/2023

OVERVIEW

Noctiva, a vasopressin analog, is indicated for the treatment of **nocturia due to nocturnal polyuria** in adults who awaken at least two times per night to void.[1] Before initiating therapy, it is recommended that the diagnosis of nocturnal polyuria has been confirmed with a 24-hour urine collection. A limitation of use is that the agent has not been studied in patients < 50 years of age.

Disease Overview

Nocturnal polyuria is defined as nocturnal urine volume exceeding 33% of the total 24-hour urine volume in patients ≥ 65 years of age or exceeding 20% of 24-hour urine volume in younger patients.[2] Nocturnal polyuria may improve via lifestyle and behavior modifications, which should be implemented prior to pharmacotherapy.[3] Such modifications include minimizing fluid intake before bed (particularly caffeine and alcohol), restriction of total fluid consumption, emptying the bladder before bed, increasing exercise and fitness levels, earlier dosing of medications such as diuretics, and elevating the legs above heart level for a few hours before going to bed (for patients with peripheral edema).

Safety

Noctiva has a Boxed Warning regarding hyponatremia.[1] Use of Noctiva is contraindicated in patients at increased risk of severe hyponatremia such as patients with excessive fluid intake, illness that may cause fluid or electrolyte imbalances, and in patients using loop diuretics or systemic or inhaled glucocorticoids. It is recommended to check serum sodium concentrations prior to initiating or resuming Noctiva and throughout treatment. If hyponatremia occurs, Noctiva may need to be temporarily or permanently discontinued. Noctiva is contraindicated in patients with hyponatremia and among those with a history of hyponatremia. Also, patients with polydipsia or primary nocturnal enuresis should not use Noctiva. Do not administer Noctiva concomitantly with loop diuretics or with systemic or inhaled glucocorticoids. Patients with renal impairment with an estimated glomerular filtration rate below 50 mL/min/1.73 m^2 should not use Noctiva. Those with known or suspected syndrome of inappropriate antidiuretic hormone secretion should not use Noctiva. Do not utilize Noctiva during illnesses that may cause fluid or electrolyte imbalance, such as gastroenteritis, salt-wasting nephropathies, or systemic infection. Noctiva is contraindicated in patients with congestive heart failure (CHF) [New York Heart Association {NYHA} class II to IV] and among those with uncontrolled hypertension because the fluid retention in these conditions increases the risk of worsening the underlying condition. Also, Noctiva is not recommended in patients at risk for increased intracranial pressure or those with a of urinary retention, and should be used with caution (e.g., monitoring of volume status) in patients with NYHA class I CHF. Noctiva is contraindicated for the treatment of primary nocturnal enuresis because of reports of hyponatremia-related seizures in pediatric patients treated with other intranasal formulations of desmopressin. Trials involving Noctiva have not been performed in pediatric patients.

Guidelines

A consensus statement on the diagnosis and treatment of nocturia was published by the International Continence Society in 2019.[2] There was consensus that fluid restriction should be advised for all desmopressin-treated patients. Newer desmopressin formulations, including Nocdurna® (desmopressin acetate sublingual tablets [27.7 mcg and 55.3 mcg]) and Noctiva, are generally regarded as low-dose desmopressin. Low-dose formulations are appropriate in the absence of contraindications to desmopressin therapy.

Oral desmopressin tablets are cited as another formulation in the consensus statement (available as 100 mcg and 200 mcg tablets in the US).[2] This is noted to be an option for certain patients, although lower-dose formulations should be used when concomitant hyponatremia risk factors are present.

Of note, it is uncertain how the pharmacokinetic profile of Noctiva aligns with the other FDA-approved nasal desmopressin products because there are no comparative bioavailability studies and Noctiva contains a novel excipient, cyclopentadecanolide, which enhances absorption.[1] The consensus statement suggests that pharmacodynamic and pharmacokinetic studies in nocturia patients during an overnight evaluation would be ideal to characterize plasma desmopressin levels and rationale for dose differentiation.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Noctiva. All approvals are provided for the duration noted below. Due to the specialized skills required for evaluation and diagnosis of patients treated with Noctiva, as well as the monitoring required for adverse events and long-term efficacy, approval requires Noctiva to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Noctiva is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Nocturia due to Nocturnal Polyuria.** Approve for 1 year if the patient meets all of the following (A, B, C, D, E, F, G and H):
1. Patient is ≥ 50 years of age; AND
1. The diagnosis of nocturnal polyuria has been confirmed with a 24-hour urine collection before treatment initiation AND the patient meets one of the following (i or ii):
1. The nocturnal urine volume exceeds 20% of the total 24-hour urine volume if the patient is < 65 years of age; OR
1. The nocturnal urine volume exceeds 33% of the total 24-hour urine volume if the patient is ≥ 65 years of age; AND
1. Prior to desmopressin therapy, patient awakens at least two times per night to void; AND
1. Patient has serum sodium concentrations within the normal range (135 to 145 mmol/L); AND
1. Prescriber has verified that the patient does not have the following conditions/circumstances in which use of Noctiva is not recommended (i, ii, iii, iv, v, or vi):
1. Currently receiving loop diuretics (e.g., furosemide, torsemide, bumetanide); OR
1. Currently receiving systemic or inhaled glucocorticoids; OR
1. Renal impairment with an estimated glomerular filtration rate < 50 mL/min/1.73 m^2; OR

1. New York Heart Association class II to IV congestive heart failure; OR
1. Polydipsia; OR
1. Known or suspected syndrome of inappropriate antidiuretic hormone secretion; AND
1. Patient has tried non-pharmacologic techniques or lifestyle interventions to manage the nocturia; AND
   Note: Examples of non-pharmacologic techniques for nocturia include nighttime fluid restriction, avoidance of caffeine and alcohol, earlier timing of medications, leg elevation, or use of compression stockings.
1. Patient tried one of Nocdurna (desmopressin acetate sublingual tablets) or oral desmopressin acetate tablets (DDAVP tablets, generic); AND
1. The medication is prescribed by or in consultation with a nephrologist, urologist, geriatrician, or endocrinologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Noctiva is not recommended in the following situations:

67. Primary Nocturnal Enuresis. Use of Noctiva is contraindicated for the treatment of patients with primary nocturnal enuresis.[1] Reports of hyponatremia-related seizures have occurred in pediatric patients treated with other intranasal formulations of desmopressin.

68. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Noctiva™ nasal spray [prescribing information]. Chesterfield, MO: Avadel; December 2017.
2. Everaert K, Hervé F, Bosch R, et al. International Continence Society consensus on the diagnosis and treatment of nocturia. *Neurourol Urodyn*. 2019;38(2):478-498.
3. Weiss JP, Everaert K. Management of nocturia and nocturnal polyuria. *Urology*. 2019;133S:24-33.

PRIOR AUTHORIZATION POLICY

POLICY: Diabetes – Continuous Glucose Monitoring Systems Prior Authorization Policy
- Dexcom G4 Platinum Continuous Glucose Monitoring (CGM) System – Dexcom
- Dexcom G5 CGM System – Dexcom
- Dexcom G6 CGM System – Dexcom
- Dexcom G7 CGM System – Dexcom
- Eversense CGM System – Ascensia/Senseonics
- Eversense E3 CGM System – Ascensia/Senseonics
- Freestyle Libre CGM System – Abbott
- Freestyle Libre 2 CGM System – Abbott
- Freestyle Libre 3 CGM System – Abbott
- Guardian Connect CGM System – Medtronic

REVIEW DATE: 01/11/2023; selected revision 11/08/2023

OVERVIEW

The products targeted in this policy are continuous glucose monitoring (CGM) systems. Freestyle Libre and Freestyle Libre 2 are considered intermittently scanned CGM (isCGM) systems, whereas the other devices are considered real-time CGM (rtCGM) systems. Of note, throughout the policy, the term CGM "system" refers to all applicable components, including sensor, transmitter/reader, and receiver.

Of note, the Dexcom G4 Platinum CGM System and the Dexcom G5 CGM System were discontinued by the manufacturer as of June 2020. Per the manufacturer, sensor supply for these systems, as well as technical support, would not be guaranteed after December 31, 2020.

Guidelines

The American Diabetes Association (ADA) Standards of Care (2023) comment on the role of rtCGM and isCGM in management of diabetes.[1] The use of rtCGM (level of evidence A) or isCGM (level of evidence B) should be offered for diabetes management in adults with diabetes on multiple daily insulin injections or continuous subcutaneous insulin infusion (CSII). These devices also should be offered in youth with diabetes on multiple daily insulin injections or CSII (level of evidence B for rtCGM in youth with type 1 diabetes; level of evidence E for other scenarios). The use of rtCGM (level of evidence A) or isCGM (level of evidence C) should also be offered for diabetes management in adults with diabetes on basal insulin. In all cases, it is noted that the choice of device should be made based on the individual's circumstances, preferences, and needs.

The American Association of Clinical Endocrinology clinical practice guidelines regarding use of advanced technology in the management of persons with diabetes mellitus (2021) discuss CGM.[2] CGM is strongly recommended for all persons with diabetes treated with intensive insulin therapy, defined as three or more injections of insulin per day or the use of an insulin pump (Grade A; high strength of evidence). It is noted that CGM may be recommended for individuals with type 2 diabetes who are treated with less intensive insulin therapy; however, the strength of evidence is lower (Grade B; intermediate strength of evidence).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of the targeted continuous glucose monitoring systems in this policy. All approvals are provided for the duration noted below.
Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of the continuous glucose monitoring systems in this policy is recommended in those who meet the following criteria:

FDA-Approved Indication

16. Diabetes. Approve for 1 year if the patient is using an insulin regimen.
Note: This includes patients on a basal insulin regimen, basal and prandial insulin regimen, or continuous subcutaneous insulin infusion (insulin pump).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of the continuous glucose monitoring systems in this policy is not recommended in the following situations:

37. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

236. American Diabetes Association. Standards of medical care in diabetes – 2023. *Diabetes Care*. 2023;46(Suppl 1):S1-S298.
237. Grunberger G, Sherr J, Allende M, et al. American Association of Clinical Endocrinology clinical practice guideline: the use of advanced technology in the management of persons with diabetes mellitus. *Endocr Pract*. 2021 Jun;27(6):505-537.

PRIOR AUTHORIZATION POLICY

POLICY: Diabetes – Glucagon-Like Peptide-1 Agonists Prior Authorization Policy

- Adlyxin® (lixisenatide subcutaneous injection – sanofi-aventis)
- Bydureon® (exenatide extended-release subcutaneous injection – AstraZeneca [obsolete 03/10/2021])
- Bydureon BCise® (exenatide extended-release subcutaneous injection – AstraZeneca)
- Byetta® (exenatide subcutaneous injection – AstraZeneca)
- Ozempic® (semaglutide subcutaneous injection – Novo Nordisk)
- Rybelsus® (semaglutide tablets – Novo Nordisk)
- Trulicity® (dulaglutide subcutaneous injection – Eli Lilly)
- Victoza® (liraglutide subcutaneous injection – Novo Nordisk)

REVIEW DATE: 10/25/2023

OVERVIEW

The glucagon-like peptide-1 (GLP-1) receptor agonists addressed in this policy are indicated as adjuncts to diet and exercise to improve glycemic control in adults with **type 2 diabetes**.[1-8] Victoza, Trulicity, and Bydureon/Bydureon BCise are additionally indicated for type 2 diabetes in patients ≥ 10 years of age.[2,3,7,8] Victoza, Ozempic, and Trulicity also have labeled indications related to cardiovascular (CV) risk reduction in adults with type 2 diabetes.[5,7,8]

Guidelines

According to the American Diabetes Association Standards of Care (2023), first-line therapy for type 2 diabetes depends on comorbidities, patient-centered treatment factors, and management needs and generally includes metformin and comprehensive lifestyle modification.[9] Among patients with type 2 diabetes with established atherosclerotic CV disease (ASCVD) or indicators of high ASCVD risk, GLP-1 agonists with proven CV disease benefit (i.e., label indication of reducing CV disease events) or a sodium glucose co-transporter-2 (SGLT-2) inhibitor are preferred regardless of baseline metformin use. A GLP-1 agonist with proven CV disease benefit is an alternative to an SGLT-2 inhibitor with primary evidence of reducing chronic kidney disease (CKD) progression if an SGLT-2 inhibitor is not tolerated or contraindicated in patients with chronic kidney disease, regardless of baseline metformin use. GLP-1 agonists are additionally recommended in patients without other cardiorenal risk factors with or without metformin based on glycemic needs. No preference is given for one GLP-1 agonist over the others; it is noted that when choosing an agent, weight loss, glycemic efficacy, administration schedule, and patient preference should be considered.

American Association of Clinical Endocrinologists statement on the comprehensive care for type 2 diabetes (2023) provides principles for the management of type 2 diabetes.[12] In patients with type 2 diabetes and established ASCVD or at high risk for ASCVD, GLP-1 agonists and SGLT-2 inhibitors are recommended. In a patient with type 2 diabetes and established ASCVD or are at high risk, a GLP-1 agonist with proven CV benefit (Ozempic, Trulicity, or Victoza) should be initiated as a first-line therapy independent of the glycemic goal or other antihyperglycemic treatments, including metformin; SGLT-2 inhibitors are an alternative. In patients with type 2 diabetes and ASCVD or at high risk of ASCVD use of a GLP-1 agonist is also recommended to reduce the risk of stroke. To reduce the risk of progression of diabetic kidney disease and CV disease in patients with type 2 diabetes SGLT-2 inhibitors are recommended; GLP-1 agonists are also an option to reduce progression of albuminuria, renal function decline, and ASCVD risk in individuals with type 2 diabetes and diabetic kidney disease (Ozempic and Trulicity are cited). For

patients with type 2 diabetes but without established or high risk for ASCVD, heart failure, stroke, or CKD, metformin should be the initial therapy unless contraindicated. In patients who are overweight or obese the following therapies are recommended and listed in order of preference: Mounjaro, GLP-1 agonists, or SGLT-2 inhibitors. In patients with a history of hypoglycemia, at high risk of hypoglycemia, or at risk of severe complications from hypoglycemia, recommended therapies (in order of preference) are: GLP-1 agonists, SGLT-2 inhibitors, Mounjaro, thiazolidinediones, and dipeptidyl peptidase-4 inhibitors.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of the GLP-1 agonists targeted in this policy. Of note, Saxenda® (liraglutide subcutaneous injection) and Wegovy® (semaglutide subcutaneous injection) are indicated for chronic weight management, not diabetes, and are not targeted in this policy. All approvals are provided for the duration noted below.

Automation: The following automation is applied in this policy:

- **Adlyxin, Byetta, Ozempic, Rybelsus:** If criteria for previous use of an oral medication for diabetes (not including Rybelsus or single-entity metformin) in the past 130 days are not met at the point of service, OR if the patient is < 18 years of age, coverage will be determined by Prior Authorization criteria.
- **Bydureon, Bydureon BCise, Trulicity, Victoza:** If criteria for previous use of an oral medication for diabetes (not including Rybelsus or single-entity metformin) in the past 130 days are not met at the point of service, OR if the patient is < 10 years of age, coverage will be determined by Prior Authorization criteria.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage is recommended in those who meet the following criteria:

FDA-Approved Indication

- **Type 2 Diabetes Mellitus.** Approve for 1 year if the patient meets one of the following (A or B):
  - Adlyxin, Byetta, Ozempic, Rybelsus: Approve if the patient is ≥ 18 years of age; OR
  - Bydureon, Bydureon BCise, Trulicity, Victoza: Approve if the patient is ≥ 10 years of age.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage is not recommended in the following situations:

38. **Weight Loss Treatment**. Saxenda contains the same chemical entity as Victoza and is indicated at a higher dose for chronic weight management. Wegovy contains the same chemical entity as Ozempic and is indicated at a higher dose for chronic weight management. Endocrine Society guidelines for pharmacological management of obesity (2015) advise against off-label prescribing of medications such as GLP-1 receptor agonists for the sole purpose of producing weight loss.[10] The American Gastroenterology Association guidelines for pharmacological interventions for adults with obesity only provide recommendations for the GLP-1 agonists approved for weight loss (i.e., Saxenda and Wegovy).[11] The GLP-1 agonists are not FDA-approved for weight loss in a patient who is overweight (body mass index [BMI] ≥ 27 kg/m^2) or obese (BMI ≥ 30 kg/m^2) without type 2 diabetes. Note: If the patient has type 2 diabetes, refer to FDA-Approved Indication.

11.

39. Type 1 Diabetes Mellitus. None of the GLP-1 agonists are indicated for patients with type 1 diabetes.[1-8] Addition of GLP-1 receptor agonists to insulin therapy resulted in small (0.2%) reductions in hemoglobin A_{1c} among patients with type 1 diabetes compared with insulin alone.[9]

40. Prediabetes/Diabetes Prevention. GLP-1 agonists are not indicated in a patient with elevated blood glucose who does not have type 2 diabetes. The American Diabetes Association Standards of Care (2023) state that metformin therapy should be considered in adults at high-risk of diabetes.[9] Further, the standards note that metformin has the longest of safety data as a pharmacologic therapy for diabetes prevention. Note: If the patient has type 2 diabetes, refer to FDA-Approved Indication.

12.

41. Metabolic Syndrome. The GLP-1 agonists are not indicated in a patient with metabolic syndrome who does not have type 2 diabetes. Note: If the patient has type 2 diabetes, refer to FDA-Approved Indication.

42. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Adlyxin® subcutaneous injection [prescribing information]. Bridgewater, NJ: sanofi-aventis; September 2023.
2. Bydureon® subcutaneous injection [prescribing information]. Wilmington, DE: AstraZeneca; December 2022.
3. Bydureon BCise® subcutaneous injection [prescribing information]. Wilmington, DE: AstraZeneca; December 2022.
4. Byetta® subcutaneous injection [prescribing information]. Wilmington, DE: AstraZeneca; December 2022.
5. Ozempic® subcutaneous injection [prescribing information]. Plainsboro, NJ: Novo Nordisk; September 2023.
6. Rybelsus® tablets [prescribing information]. Plainsboro, NJ: Novo Nordisk; January 2023.
7. Trulicity® subcutaneous injection [prescribing information]. Indianapolis, IN: Lilly; November 2022.
8. Victoza® subcutaneous injection [prescribing information]. Plainsboro, NJ: Novo Nordisk; July 2023.
9. American Diabetes Association. Standards of medical care in diabetes – 2023. *Diabetes Care*. 2023;46(Suppl 1):S1-S291.
10. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(2):342-362.
11. Grunvald E, Shah R, Hernaez R, et al. AGA clinical practice guideline on pharmacological interventions for adults with obesity. *Gastroenterol*. 2022;163:1198-1225.
12. Samson SL, Vellanki P, Blonde L, et al. American Association of Clinical Endocrinology consensus statement: comprehensive type 2 diabetes management algorithm – 2023 update. *Endocr Pract*. 2023;29:305-340.

PRIOR AUTHORIZATION POLICY

POLICY: Diabetes – Kerendia Prior Authorization Policy
- Kerendia™ (finerenone tablets – Bayer)

REVIEW DATE: 08/02/2023

OVERVIEW

Kerendia, a nonsteroidal mineralocorticoid receptor antagonist (MRA), is indicated in adults with **chronic kidney disease (CKD) associated with type 2 diabetes** to the reduce the risk of sustained estimated glomerular filtration rate (eGFR) decline, end-stage kidney disease, cardiovascular (CV) death, non-fatal myocardial infarction, and hospitalization for heart failure.[1]

Per the prescribing information, do not initiate treatment with Kerendia if serum potassium is > 5.0 mEq/L.[1] Additionally, initiation of Kerendia is not recommended in patients with eGFR < 25 mL/min/1.73 m^2. Kerendia labeling includes a Warning regarding hyperkalemia and notes that the risk increases with decreasing kidney function. Monitoring of serum potassium and eGFR is recommended.

Clinical Efficacy

Efficacy of Kerendia was evaluated in two Phase III, placebo-controlled trials, FIDELIO-DKD (published) [n = 5,734] and FIGARO-DKD (published) [n = 7,352].[2,8] All patients were required to be treated with an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) at the maximum tolerated labeled dose for ≥ 4 weeks prior to the run-in visit. Additionally, patients were required to have a urinary albumin-to-creatinine ratio of ≥ 30 mg/g, in addition to other renal entry criteria.

Guidelines

The American Diabetes Association (ADA) Standards of Care (2023) recommend Kerendia for patients with type 2 diabetes and CKD treated with maximum tolerated doses of ACE inhibitors or ARBs, to improve CV outcomes and reduce the risk of CKD progression (level A recommendation).[3] Additionally, in the section regarding CKD (Chapter 11), it is noted that in patients with diabetic kidney disease and type 2 diabetes, use of sodium glucose co-transporter-2 inhibitors (if eGFR is ≥ 20 mL/min/1.73 m^2), a glucagon-like peptide-1 agonist, or Kerendia (if eGFR is ≥ 25 mL/min/1.73 m^2), should be considered for CV risk reduction (level A recommendation). In patients with CKD and albuminuria, who are at increased risk for CV events or CKD progression, Kerendia is recommended to reduce CKD progression and CV events (level A recommendation).

The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Diabetes Management in CKD (2022) suggests use of Kerendia in patients with type 2 diabetes with eGFR ≥ 25 mL/min/1.73 m^2, normal serum potassium, and albuminuria (≥ 30 mg/g) despite maximal tolerated doses of a renin-angiotensin-aldosterone system (RAAS) inhibitor.[4] The rationale for adding an MRA to current standard of care, including ACE inhibitor or ARB, is that this combination has been proven to be an effective strategy to reduce albuminuria in patients with diabetes and CKD. The steroidal MRAs, spironolactone and eplerenone, have been shown to effectively reduce albuminuria; however, there are not data demonstrating that these agents reduce the risk of clinical outcomes. Kerendia reduces albuminuria and the risk of kidney and CV outcomes. The guidelines also note that Kerendia is most appropriate for patients with type 2 diabetes who are at high risk of CKD progression and CV events, because Kerendia can be added to an ACE/ARB and a sodium glucose co-transporter-2 inhibitor for treatment of type 2 diabetes and CKD.

A consensus report from the ADA/KDIGO (2022) for diabetes management in CKD states that Kerendia is recommended for patients with type 2 diabetes, eGFR ≥ 25 mL/min/1.73 m^2, normal serum potassium concentration, and albuminuria (albumin:creatinine ratio ≥ 30 g/g) despite a maximum tolerated dose of RAAS inhibitor therapy.[10]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Kerendia. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kerendia recommended in those who meet the following criteria:

FDA-Approved Indication

17. Diabetic Kidney Disease. Approve for 1 year if the patient meets the following (A or B):

- **A)** Initial Therapy. Approve if the patient meets the following (i, ii, iii, and iv):
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** Patient has a diagnosis of type 2 diabetes; AND
  - **iii.** Patient meets one of the following (a or b):
    - **a)** Patient is currently receiving a maximally tolerated labeled dosage of an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB); OR
    - **b)** According to the prescriber, patient has a contraindication to ACE inhibitor and ARB therapy; AND
  - **iv.** At baseline (prior to the initiation of Kerendia), patient meets all of the following (a, b, and c):
    - **a)** Estimated glomerular filtration rate ≥ 25 mL/min/1.73 m^2; AND
    - **b)** Urine albumin-to-creatinine ratio ≥ 30 mg/g; AND
    - **c)** Serum potassium level ≤ 5.0 mEq/L.
- **B)** Patient is Currently Receiving Kerendia. Approve if the patient meets the following (i, ii, and iii):
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** Patient has a diagnosis of type 2 diabetes; AND
  - **iii.** Patient meets one of the following (a or b):
    - **a)** Patient is currently receiving a maximally tolerated labeled dosage of an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB); OR
    - **b)** According to the prescriber, patient has a contraindication to ACE inhibitor and ARB therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kerendia not recommended in the following situations:

43. Heart Failure (Treatment). Patients with a clinical diagnosis of heart failure with reduced ejection fraction (New York Heart Association [NYHA] Class II through IV) were excluded from FIDELIO-DKD and FIGARO-DKD.[2,8] Kerendia was compared with eplerenone in the Phase IIb ARTS-HF trial (n = 1,066) among patients with heart failure with reduced ejection fraction and type 2 diabetes and/or chronic kidney disease.[5] The primary endpoint was proportion of patients with > 30% decline in N-

terminal pro-B-type natriuretic peptide (NT-proBNP) at Day 90. Kerendia induced a > 30% decrease in NT-proBNP levels in a similar proportion of patients compared with eplerenone. Further data are needed to characterize the role of Kerendia in chronic heart failure management. Kerendia is not addressed in heart failure guidelines. In an update to American College of Cardiology heart failure guidelines (2022), MRAs (spironolactone, eplerenone) are recommended in patients with heart failure with reduced ejection fraction and NYHA Class II to IV symptoms, if eGFR is > 30 mL/min/1.73 m^2 and serum potassium is < 5 mEq/L.[6] MRAs are also among the classes which may be considered for heart failure with mildly reduced ejection fraction and in selected patients with heart failure with preserved ejection fraction. An American College of Cardiology Expert Consensus Decision Pathway on Management of Heart Failure with Preserved Ejection Fraction (2023) lists Kerendia as a medication for patients with heart failure with preserved ejection fraction with concomitant diabetes and diabetic kidney disease.[9] The American Diabetes Association Standards of Care (2023) note that the pooled FIDELITY trial analysis confirms and strengthens the positive cardiovascular and renal outcomes with Kerendia across the spectrum of chronic kidney disease, irrespective of baseline atherosclerotic cardiovascular disease (with the *exclusion* of those with heart failure with reduced ejection fraction).[3]
Note: For a patient with concomitant diabetic kidney disease and heart failure, refer to FDA-Approved Indication.

44. Hypertension (Treatment). Kerendia has not been evaluated for use in essential hypertension and is not mentioned in American College of Cardiology/American Heart Association hypertension guidelines (2017).[7] Spironolactone and eplerenone are cited as secondary agents for management of hypertension and are noted to be common add-on therapies for resistant hypertension. Primary agents include thiazide diuretics, ACE inhibitors, ARBs, and calcium channel blockers.
Note: For a patient with concomitant diabetic kidney disease and hypertension, refer to FDA-Approved Indication.

45. Concomitant Use with Spironolactone or Eplerenone. Spironolactone and eplerenone are steroidal mineralocorticoid receptor antagonists. Based on their mechanism of action, an increase in adverse events (e.g., hyperkalemia) would be expected if used concomitantly with Kerendia. Concomitant spironolactone or eplerenone use was not permitted in clinical trials.

46. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Diabetes – Mounjaro Prior Authorization Policy
- Mounjaro™ (tirzepatide subcutaneous injection – Lilly)

REVIEW DATE: 06/07/2023; selected revision 07/05/2023

OVERVIEW

Mounjaro, a glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) agonist, is indicated as an adjunct to diet and exercise to improve glycemic control in adults with **type 2 diabetes mellitus**.

Guidelines

According to the American Diabetes Association Standards of Care (2023), regarding pharmacologic therapy for adults with type 2 diabetes, a patient-centered approach should guide the choice of agents.[2] Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, risk for adverse events (AEs), and patient preferences. Of note, for patients with type 2 diabetes, a GLP-1 agonist is preferred over insulin when possible. Further, if insulin is used, combination therapy with a GLP-1 agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. The very high glycemic efficacy of the GLP-1 agonists (cited as semaglutide and Trulicity® [dulaglutide injection]) and Mounjaro are recognized. The American Association of Clinical Endocrinologists provide similar recommendaitons.[3,4]

An American College of Cardiology Consensus Pathway on the management of heart failure with preserved ejection fraction (HFpEF) cites substantial weight loss with Mounjaro and semaglutide in patients with type 2 diabetes and obesity and notes promising data with Mounjaro as well as other GLP-1 agonists based on their weight loss potential.[5] Although the findings are encouraging, neither product has been rigorously studied in patients with heart failure, and concerns over loss of lean muscle mass in patients with heart failure are noted. Ongoing studies with each product will provide more information in patients with HFpEF.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Mounjaro. All approvals are provided for the duration noted below.

Automation: If criteria for a previous use of an oral medication for diabetes (not including Rybelsus® [semaglutide tablets] or single-entity metformin) in the past 130 days are not met at the point of service, OR if the patient is < 18 years of age, coverage will be determined by Prior Authorization criteria.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mounjaro is recommended in those who meet the following criteria:

FDA-Approved Indication

18. Type 2 Diabetes Mellitus. Approve for 1 year if the patient is ≥ 18 years of age.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mounjaro is not recommended in the following situations:

47. **Weight Loss.** Mounjaro is not FDA-approved for weight loss in a patient who is overweight (body mass index [BMI] ≥ 27 kg/m^2) or obese (BMI ≥ 30 kg/m^2) without type 2 diabetes. Clinical trials in a patient who is overweight or obese are ongoing. Note: If the patient has type 2 diabetes, refer to FDA-Approved Indication.

48. **Type 1 Diabetes Mellitus.** Mounjaro is not indicated for type 1 diabetes. Clinical trials excluded patients with type 1 diabetes.

49. **Prediabetes/Diabetes Prevention.** Mounjaro is not indicated in a patient with elevated blood glucose who does not have type 2 diabetes. The American Diabetes Association Standards of Care (2023) state that metformin therapy should be considered in adults at high-risk of diabetes.[2] Further, the standards note that metformin has the longest of safety data as a pharmacologic therapy for diabetes prevention. Note: If the patient has type 2 diabetes, refer to FDA-Approved Indication.

50. **Metabolic Syndrome.** Monjauro is not indicated in a patient with metabolic syndrome who does not have type 2 diabetes. Note: If the patient has type 2 diabetes, refer to FDA-Approved Indication.

51. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Diabetes – Symlin Prior Authorization Policy
- Symlin® (pramlintide subcutaneous injection – AstraZeneca)

REVIEW DATE: 08/09/2023

OVERVIEW

Symlin, an antihyperglycemic agent, is indicated as an adjunctive treatment in patients with **type 1 or type 2 diabetes** who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.[1]

Guidelines/Consensus Statements

The American Diabetes Association Standards of Medical Care in Diabetes (2023) do not provide a specific recommendation for use of Symlin in type 1 or type 2 diabetes.[2] The American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for developing a comprehensive care plan (2022) recommend adding a glucagon-like peptide-1 agonist, a sodium glucose co-transporter-2 inhibitor, or Symlin (less commonly used) to reduce postprandial hyperglycemia, hemoglobin A_{1c}, and weight in individuals with type 2 diabetes who are treated with basal-bolus insulin therapy.[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Symlin. All approvals are provided for the duration noted below.

Automation: If criteria for previous use of insulin (automated) within the past 130 days are not met at the point of service, coverage will be determined by prior authorization criteria.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Symlin is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Diabetes Mellitus, Type 1 or Type 2.** Approve for 1 year if Symlin is prescribed in adjunct to insulin therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Symlin is not recommended in the following situations:

1. **Weight Loss Treatment**. American Association of Clinical Endocrinologists/American College of Endocrinology obesity clinical practice guidelines (2016) comment that Symlin may lead to modest weight loss in diabetic patients but do not comment on a role for Symlin in management of obesity in non-diabetic patients.[5] Guidelines from the American Gastroenterological Association (2022) do not address Symlin for weight loss.[6] Other pharmacotherapies are available and indicated for weight loss.
2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Diabetes – Tzield Prior Authorization Policy
- Tzield™ (teplizumab-mzwv intravenous infusion – Provention/Sanofi)

REVIEW DATE: 11/15/2023

OVERVIEW

Tzield, an anti-CD3 monoclonal antibody, is indicated to **delay the onset of Stage 3 type 1 diabetes** in adults and pediatric patients ≥ 8 years of age with Stage 2 type 1 diabetes.[1]

Tzield is administered by intravenous infusion (over a minimum of 30 minutes) using body surface area-based dosing, once daily for 14 consecutive days.[1] Prior to initiating Tzield, obtain a complete blood count and liver enzyme tests. Use of Tzield is not recommended in patients with certain laboratory abnormalities, including lymphopenia, anemia, thrombocytopenia, neutropenia, or increased liver enzymes. Refer to the prescribing information for specific thresholds. Additionally, patients with laboratory or clinical evidence of acute infection with Epstein-Barr virus or cytomegalovirus should not receive Tzield, nor should patients with active serious infection or chronic active infection other than localized skin infections.

Clinical Efficacy

Efficacy of Tzield among patients at risk for development of type 1 diabetes was evaluated in one pivotal study called TN-10 (published) [n = 76].[2] Eligible patients were non-diabetic relatives of patients with type 1 diabetes and were ≥ 8 years of age at the time of randomization. Patients were also required to have two or more diabetes-related autoantibodies, confirmed on at least two occasions, within 6 months before randomization. In addition, patients were required to have had evidence of dysglycemia during an oral glucose tolerance test (OGTT). An abnormal OGTT was defined as meeting one of the following: fasting plasma glucose ≥ 110 to < 126 mg/dL; 2-hour postprandial plasma glucose ≥ 140 to < 200 mg/dL; or 30-, 60-, or 90-minute postprandial plasma glucose ≥ 200 mg/dL. Initially, two OGTTs were required within 52 days of enrollment; however, a protocol amendment was put in place requiring only one abnormal glucose tolerance test result for patients < 18 years of age.

Guidelines

American Diabetes Association (ADA) Standards of Care (2023) state that Tzield should be considered in selected individuals ≥ 8 years with stage 2 type 1 diabetes to delay the onset of symptomatic type 1 diabetes.[3] Management should be in a specialized setting with appropriately trained personnel. According to the ADA Standards, screening for pre-symptomatic type 1 diabetes may be done by detection of autoantibodies to insulin, glutamic acid decarboxylase (GAD, GAD65), islet antigen 2 (IA-2 and IA-2b), or zinc transporter 8 (Level B recommendation).[3] The presence of multiple islet autoantibodies is a risk factor for clinical diabetes. Testing for dysglycemia may be used to further forecast near-term risk. When multiple islet autoantibodies are identified, referral to a specialized center for further evaluation and/or consideration of a clinical trial or approved therapy to potentially delay the development clinical diabetes should be considered (Level B recommendation).

According to the ADA Standards, three distinct stages of type 1 diabetes can be identified, which serve as a framework for future research and regulatory decision-making.[3] Clinical type 1 diabetes is referred to as "Stage 3 type 1 diabetes" and is characterized by overt hyperglycemia and the presence of symptoms. Diagnostic criteria include involve one of the following: fasting plasma glucose (FPG) ≥ 126 mg/dL; 2-

hour postprandial glucose ≥ 200 mg/dL during an OGTT (75 grams); hemoglobin A_{1c} (HbA_{1c}) ≥ 6.5%; or random plasma glucose ≥ 200 mg/dL for a patient with classic symptoms of hyperglycemia or hyperglycemic crisis. "Stage 1 type 1 diabetes" and "Stage 2 type 1 diabetes" are pre-symptomatic states characterized by autoimmunity (i.e., multiple autoantibodies) but no overt diabetes symptoms. In Stage 1 disease, glycemia is normal. In Stage 2 disease, dysglycemia is present but below the threshold considered overt for Stage 3 type 1 diabetes. Dysglycemia in Stage 2 type 1 diabetes involves FPG 100 to 125 mg/dL; 2-hour postprandial glucose 140 to 199 mg/dL; HbA_{1c} 5.7% to 6.4%; or a ≥ 10% increase in HbA_{1c}.

Screening for Type 1 Diabetes Risk

Multiple studies indicate that measuring islet autoantibodies in relatives of those with type 1 diabetes or in children from the general population can effectively identify those who will develop type 1 diabetes.[3] A study reported the risk of progression to type 1 diabetes from the time of seroconversion to autoantibody positivity in pediatric cohorts from three countries. Of the 585 children who developed more than two autoantibodies, nearly 70% developed type 1 diabetes within 10 years and 84% developed type 1 diabetes within 15 years. These findings are highly significant because while the one group of patients was recruited from children of parents with type 1 diabetes, the other two groups were recruited from the general population. The findings in all three groups were the same, suggesting that the same sequence of events led to clinical disease in both "sporadic" and familial cases of type 1 diabetes. The risk of type 1 diabetes increases as the number of relevant autoantibodies detected increases.

Family history of autoimmune diabetes and personal or family history of allergic diseases or other autoimmune diseases increases risk of autoimmune diabetes compared with the general population.[3] Individuals who test autoantibody positive should be either provided with or referred for counseling about the risk of developing diabetes, diabetes symptoms, diabetic ketoacidosis prevention, and consideration of additional testing as applicable to help determine if they meet criteria for intervention aimed at delaying progression.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tzield. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tzield as well as the monitoring required for adverse events and long-term efficacy, approval requires Tzield to be prescribed by or in consultation with a physician who specializes in the condition being treated. For certain criteria, verification is required as noted by **[verification required by prescriber]**. All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to chart notes, laboratory tests, claims records, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tzield is recommended in those who meet the following criteria:

FDA-Approved Indication

19. **Type 1 Diabetes (Clinical/Stage 3), Delay of Onset.** Approve for a one-time per lifetime course (14-day course) if the patient meets the following (A, B, C, D, E, F, G, H, I, J, and K):

A) Patient is ≥ 8 years of age; AND

B) Patient does NOT have a clinical diagnosis of type 1 diabetes (i.e., Stage 3 type 1 diabetes); AND
Note: Clinical type 1 diabetes is also referred to as Stage 3 type 1 diabetes. "Stage 1 type 1 diabetes" and "Stage 2 type 1 diabetes" are considered preclinical states and would not fall into the category of clinical type 1 diabetes.

C) Patient does NOT have type 2 diabetes; AND

D) Patient has at least one biological relative with a diagnosis of type 1 diabetes; AND
Note: Examples of relatives include first-degree relatives (e.g., parent, sibling) or other relatives (e.g., grandparent, aunt, uncle, cousin).

E) Patient has tested positive for at least TWO of the following type 1 diabetes-related autoantibodies on two separate occasions: anti-glutamic acid decarboxylase 65 (anti-GAD65); anti-islet antigen-2 (anti-IA-2); islet-cell autoantibody (ICA); micro insulin; anti-zinc transporter 8 (anti-ZnT8) **[documentation required]**.
Note: The patient needs to have tested positive on two separate occasions, with at least two positive autoantibodies per occasion; however, the patient does not have to be positive for the same two antibodies on both occasions. For example, a positive test for anti-GAD65 and anti-IA-2 on one occasion, and positive test for ICA and micro insulin on another occasion would satisfy the requirement.

F) Patient meets ONE of the following (i, ii, or iii) **[documentation required]**:
- **i.** Patient has a 2-hour postprandial glucose level ≥ 140 to < 200 mg/dL during an oral glucose tolerance test in the preceding 2 months; OR
- **ii.** Patient has a fasting plasma glucose level ≥ 100 to < 126 mg/dL in the preceding 2 months; OR
- **iii.** Patient has an HbA_{1c} ≥ 5.7% to < 6.5% in the preceding 2 months. AND

G) At baseline (prior to the initiation of Tzield), patient does NOT have evidence of hematologic compromise, as defined by meeting the following (i, ii, iii, and iv) **[documentation required]**:
- **i.** Lymphocyte count ≥ 1,000 lymphocytes/mcL; AND
- **ii.** Hemoglobin ≥ 10 g/dL; AND
- **iii.** Platelet count ≥ 150,000 platelets/mcL; AND
- **iv.** Absolute neutrophil count ≥ 1,500 neutrophils/mcL; AND

H) At baseline (prior to the initiation of Tzield), patient does NOT have evidence of hepatic compromise, as defined by meeting the following (i, ii, and iii) **[documentation required]**:
- **i.** Alanine aminotransferase (ALT) ≤ 2 times the upper limit of normal (ULN); AND
- **ii.** Aspartate aminotransferase (AST) ≤ 2 times the ULN; AND
- **iii.** Bilirubin ≤ 1.5 times the ULN; AND

I) According to the prescriber, the patient does NOT have any of the following (i, ii, or iii):
- **i.** Laboratory or clinical evidence of acute infection with Epstein-Barr Virus or cytomegalovirus; OR
- **ii.** Active serious infection; OR
- **iii.** Chronic active infection (other than localized skin infection); AND

J) Patient has NOT received Tzield in the past **[verification required by prescriber]**; AND
Note: Verify through claims that the patient has not previously received Tzield AND, if no claim for Tzield is present, the prescriber must attest that the patient has not previously received Tzield.

K) The medication will be prescribed by an endocrinologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tzield is not recommended in the following situations:

52. Type 1 Diabetes (Clinical/Stage 3), Treatment. Note: Clinical type 1 diabetes is also referred to as Stage 3 type 1 diabetes. "Stage 1 type 1 diabetes" and "Stage 2 type 1 diabetes" are considered preclinical states and would not fall into the category of clinical type 1 diabetes.
Tzield is not indicated for patients with a diagnosis of clinical type 1 diabetes (i.e., Stage 3 type 1 diabetes).

53. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Dichlorphenamide Prior Authorization Policy
- Keveyis® (dichlorphenamide tablets – Xeris, generic)

REVIEW DATE: 01/03/2024

OVERVIEW

Dichlorphenamide, a carbonic anhydrase inhibitor, is indicated for the treatment of **primary hyperkalemic periodic paralysis** (HyperPP), **primary hypokalemic periodic paralysis** (HypoPP), and related variants.[1] These conditions are heterogeneous and response to dichlorphenamide may vary; therefore, prescribers should evaluate the patient's response to dichlorphenamide after 2 months to decide whether it should be continued.

Disease Overview

The primary periodic paralyses are rare muscle disorders caused by autosomal dominant genetic mutations in ion channels.[2,3] The altered channels cannot properly regulate the flow of ions into muscle cells, which reduces the ability of skeletal muscles to contract, leading to severe muscle weakness or paralysis.[4] Genetic testing is recommended as the first diagnostic step; a heterozygous pathogenic mutation can be identified in 60% to 70% of periodic paralysis cases.[5] When a genetic mutation cannot be identified, periodic paralyses can be distinguished based on clinical presentation. Other causes of hypokalemia or hyperkalemia should be excluded.[5]

Regarding treatment, oral potassium salts can be taken as maintenance/prophylactic therapy for patients with HypoPP; however, this does not completely prevent attacks.[6] Although data are limited to case reports and single-blind trials, acetazolamide, another carbonic anhydrase inhibitor, has been used historically for primary periodic paralysis. Acetazolamide treatment is beneficial in approximately 50% of patients with HypoPP and it has no effect in 30% of affected patients. It can also exacerbate symptoms in 20% of patients. Dichlorphenamide has been reported to be 30 times more potent than acetazolamide in vitro.[7] Prior to initiating dichlorphenamide it is important to verify if the patient has had exacerbation with acetazolamide, since dichlorphenamide is considered to be more potent and may potentially lead to more exacerbations.[8]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of dichlorphenamide. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with dichlorphenamide, as well as the monitoring required for adverse events and long-term efficacy, initial approval requires dichlorphenamide to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of dichlorphenamide is recommended in those who meet one of the following criteria:

FDA-Approved Indications

26. Hypokalemic Periodic Paralysis (HypoPP) and Related Variants. Approve for the duration noted if the patient meets one of the following criteria (A or B):

- Initial Therapy. Approve for 2 months if the patient meets the following (i, ii, iii, iv, v, and vi):
    - Patient has a confirmed diagnosis of primary hypokalemic periodic paralysis by meeting at least ONE of the following (a, b, or c):
        - Patient has had a serum potassium concentration of less than 3.5 mEq/L during a paralytic attack; OR
        - Patient has a family history of the condition; OR
        - Patient has a genetically confirmed skeletal muscle calcium or sodium channel mutation; AND
    - The prescriber has excluded other reasons for acquired hypokalemia; AND

    Z) Note: Examples of other reasons for acquired hypokalemia include renal, adrenal, or thyroid dysfunction; renal tubular acidosis; and diuretic or laxative abuse.
    - Patient has had improvements in paralysis attack symptoms with potassium intake; AND
    - Patient has tried oral acetazolamide therapy; AND
    - According to the prescriber, acetazolamide therapy did not worsen the paralytic attack frequency or severity in the patient; AND
    - The medication is prescribed by or in consultation with a neurologist or a physician who specializes in the care of patients with primary periodic paralysis (e.g., muscle disease specialist, physiatrist); OR
- Patient is Currently Receiving Dichlorphenamide. Approve for 1 year if the patient has responded to dichlorphenamide (e.g., decrease in the frequency or severity of paralytic attacks) as determined by the prescriber.

27. Hyperkalemic Periodic Paralysis (HyperPP) and Related Variants. Approve for the duration noted if the patient meets one of the following (A or B):

- Initial Therapy. Approve for 2 months if the patient meets the following (i, ii, iii, iv and v):
    - Patient has a confirmed diagnosis of primary hyperkalemic periodic paralysis by meeting at least ONE of the following criteria (a, b, c, or d):
        - Patient has had an increase from baseline in serum potassium concentration of greater than or equal to 1.5 mEq/L during a paralytic attack; OR
        - Patient has had a serum potassium concentration during a paralytic attack of greater than 5.0 mEq/L; OR
        - Patient has a family of the condition; OR
        - Patient has a genetically confirmed skeletal muscle sodium channel mutation; AND
    - The prescriber has excluded other reasons for acquired hyperkalemia; AND

    AA) Note: Examples of other reasons for acquired hyperkalemia include drug abuse, renal dysfunction, and adrenal dysfunction.
    - Patient has tried oral acetazolamide therapy; AND
    - According to the prescriber, acetazolamide therapy did not worsen the paralytic attack frequency or severity in the patient; AND
    - The medication is prescribed by or in consultation with a neurologist or a physician who specializes in the care of patients with primary periodic paralysis (e.g., muscle disease specialist, physiatrist); OR
- Patient is Currently Receiving Dichlorphenamide. Approve for 1 year if the patient has responded to dichlorphenamide (e.g., decrease in the frequency or severity of paralytic attacks) as determined by the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of dichlorphenamide is not recommended in the following situations:

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Dronabinol Products Prior Authorization with Step Therapy Policy
- Marinol® (dronabinol capsules – ThePharmaNetwork, generic)
- Syndros® (dronabinol oral solution – Insys/Benuvia)

REVIEW DATE: 11/15/2023

OVERVIEW

Dronabinol capsules and Syndros are cannabinoids indicated for the following uses[1,2]:
- **Anorexia associated with weight loss**, in patients with Acquired Immune Deficiency Syndrome (AIDS).
- **Nausea and vomiting associated with cancer chemotherapy**, in patients who have failed to respond adequately to conventional antiemetic treatments.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines regarding the treatment of emesis (version 2.2023 – May 24, 2023) include various antiemetic regimens depending upon the emetogenic potential of the chemotherapy agent(s) being administered.[3] For breakthrough emesis, the guidelines recommend adding an agent from a different drug class to the current regimen, but no preference is given among specific products. Dronabinol is included in the list of medications for breakthrough nausea or emesis. Other recommended agents for breakthrough nausea or emesis include serotonin receptor antagonists, olanzapine, lorazepam, haloperidol, metoclopramide, scopolamine, prochlorperazine, promethazine, and dexamethasone.

POLICY STATEMENT

2. Prior Authorization is recommended for prescription benefit coverage of dronabinol products. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of dronabinol capsules is recommended in those who meet one of the following criteria:

FDA-Approved Indications

22. Anorexia Associated with Weight Loss in a Patient with Acquired Immune Deficiency Syndrome (AIDS). Approve for 6 months if the patient meets ONE of the following (A or B):
- **A)** Generic dronabinol capsules are requested; OR
- **B)** If brand Marinol is prescribed, the patient meets BOTH of the following (i and ii):
  - **i.** Patient has tried generic dronabinol capsules; AND
  - **ii.** The Brand product is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the

bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

2. **Nausea and Vomiting Associated with Cancer Chemotherapy.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient has failed to respond adequately to at least TWO conventional antiemetic treatments; AND
   Note: Examples of conventional antiemetic treatments include selective serotonin [5-HT_3] receptor antagonists (such as ondansetron, granisetron, Anzemet [dolasetron], Aloxi [palonosetron injection]), Akynzeo (netupitant/palonosetron capsules), Emend (aprepitant capsules), Varubi (rolapitant tablets), metoclopramide, prochlorperazine, dexamethasone, olanzapine.
   B) Patient meets ONE of the following (i or ii):
      i. Generic dronabinol capsules are requested; OR
      ii. If brand Marinol is prescribed, the patient meets BOTH of the following (a and b):
         a) Patient has tried generic dronabinol capsules; AND
         b) The Brand product is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

II. Coverage of Syndros is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Anorexia Associated with Weight Loss in a Patient with Acquired Immune Deficiency Syndrome (AIDS).** Approve for 6 months if the patient meets ONE of the following (A or B):
   A) Patient has tried generic dronabinol capsules; OR
   B) Patient cannot swallow or has difficulty swallowing capsules.

2. **Nausea and Vomiting Associated with Cancer Chemotherapy.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient has failed to respond adequately to at least TWO conventional antiemetic treatments; AND
   Note: Examples of conventional antiemetic treatments include selective serotonin [5-HT_3] receptor antagonists (such as ondansetron, granisetron, Anzemet [dolasetron], Aloxi [palonosetron injection]), Akynzeo (netupitant/palonosetron capsules), Emend (aprepitant capsules), Varubi (rolapitant tablets), metoclopramide, prochlorperazine, dexamethasone, olanzapine.
   B) Patient meets ONE of the following (i or ii):
      i. Patient has tried generic dronabinol capsules; OR
      ii. Patient cannot swallow or has difficulty swallowing capsules.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of dronabinol products is not recommended in the following situations:

4. **Chronic Non-Cancer Pain.** Based on a review of published studies, there is insufficient evidence for the use of dronabinol in non-cancer pain due to the small study sizes and moderate to high risk of bias to allow for a definitive conclusion.[4] In the two studies reviewed, the authors reported mixed effects for pain measures for dronabinol. More data are needed to define the place in therapy of dronabinol in the treatment of chronic non-cancer pain.

5. **Multiple Sclerosis.** Results from one published, randomized, double-blind, placebo-controlled study (n = 498) demonstrated that dronabinol has no overall effect on the progression of multiple sclerosis in patients with primary and secondary progressive multiple sclerosis.[5] More data are needed to define the place in therapy of dronabinol in the treatment of multiple sclerosis.
2.
6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.
3.
4.

REFERENCES

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93. Syndros® oral solution [prescribing information]. Round Rock, TX: Benuvia Therapeutics; September 2022.
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95. Butler M, Krebs E, Sunderlin B, Kane R. Medical cannabis for non-cancer pain: a systematic review. (Prepared by Minnesota Evidence-based Practice Center.) 2016. Available at: https://www.health.state.mn.us/people/cannabis/docs/intractable/medicalcannabisreport.pdf. Accessed on November 9, 2023.
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PRIOR AUTHORIZATION POLICY

POLICY: Enspryng Prior Authorization Policy
- Enspryng® (satralizumab-mwge subcutaneous injection – Genentech)

REVIEW DATE: 09/20/2023

OVERVIEW

Enspryng, an interleukin-6 receptor antagonist, is indicated for the treatment of **neuromyelitis optica spectrum disorder** (NMOSD) in adults who are anti-aquaporin-4 antibody positive.[1]

Disease Overview

NMOSD is a rare, relapsing, autoimmune disorder of the brain and spinal cord with optic neuritis and/or myelitis as predominant characteristic symptoms.[2] NMOSD often causes significant, permanent damage to vision and/or spinal cord function resulting in blindness or impaired mobility.[3] Patients may experience pain, paralysis, loss of bowel and bladder control, loss of visual acuity, and uncontrolled motor functions. Complications can lead to death.

Other Therapies

Soliris® (eculizumab intravenous infusion) and Uplizna™ (inebilizumab-cdon intravenous infusion) are two other FDA-approved medications for treatment of NMOSD.[4,5] For acute attacks, typical treatment is high-dose intravenous corticosteroids.[6,7] Plasma exchange may be effective in patients who suffer acute severe attacks that do not respond to intravenous corticosteroids. For long-term control of the disease, a variety of immunosuppressive drugs are utilized as first-line therapy. Preventative maintenance therapies include corticosteroids, azathioprine, mycophenolate mofetil, and rituximab (off-label).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Enspryng. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Enspryng as well as the monitoring required for adverse events and long-term efficacy, approval requires Enspryng to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Enspryng is recommended in those who meet the following criteria:

FDA-Approved Indication

28. Neuromyelitis Optica Spectrum Disorder. Approve for the duration noted if the patient meets ONE of the following (A or B):

C) Initial Therapy. Approve for 1 year if the patient meets the following (i, ii, iii, iv, and v):

vi. Patient is ≥ 18 years of age; AND

vii. Diagnosis was confirmed by a positive blood serum test for anti-aquaporin-4 antibody; AND

viii. Patient is currently receiving or has previously tried TWO of the following systemic therapies (a, b, c, or d):
- **a)** Azathioprine; OR
- **b)** Corticosteroid; OR
- **c)** Mycophenolate mofetil; OR
- **d)** Rituximab; AND

Note: An exception to the requirement for a trial of a systemic therapy can be made if the patient has already tried Soliris (eculizumab intravenous infusion) or Uplizna (inebilizumab-cdon intravenous infusion) for neuromyelitis optica spectrum disorder. Patients who have already tried Soliris or Uplizna for neuromyelitis optica spectrum disorder are not required to try another systemic agent.

ix. Patient has a of at least one relapse in the last 12 months or two relapses in the last 2 years; AND

x. The medication is being prescribed by or in consultation with a neurologist.

D) Patient is Currently Receiving Enspryng. Approve for 1 year if the patient meets the following (i, ii, iii, and iv):

v. Patient is ≥ 18 years of age; AND

vi. Diagnosis was confirmed by a positive blood serum test for anti-aquaporin-4 antibody; AND

vii. According to the prescriber, patient has had clinical benefit from the use of Enspryng; AND

Note: Examples of clinical benefit include reduction in relapse rate, reduction in symptoms (e.g., pain, fatigue, motor function), and a slowing in progression of symptoms.

viii. The medication is being prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Enspryng is not recommended in the following situations:

54. Concomitant Use with a Rituximab Product, Soliris (eculizumab intravenous infusion), or Uplizna (inebilizumab-cdon intravenous infusion). There is no evidence to support concomitant use of Enspryng with a rituximab product, Soliris or Uplizna.

55. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Aldurazyme Prior Authorization Policy
- Aldurazyme® (laronidase intravenous infusion – Genzyme)

REVIEW DATE: 04/12/2023

OVERVIEW

Aldurazyme, a human α-L-iduronidase, is indicated for patients with **Hurler and Hurler-Scheie forms of Mucopolysaccharidosis type I** (MPS I) and in patients with the **Scheie form who have moderate to severe symptoms**.[1]

Disease Overview

MPS I is a rare autosomal recessive, lysosomal storage disease characterized by the deficiency of α-L-iduronidase.[2] Patients with MPS I are unable to degrade dermatan and heparin sulfate, resulting in the accumulation of glycosoaminoglycans within lysosomes. Over time, the accumulation of glycosoaminoglycans leads to progressive tissue damage,[3] ultimately resulting in multiorgan dysfunction.[2,3] Patients with MPS I commonly have a characteristic face, corneal clouding, cardiomyopathy, enlarged tongue, respiratory insufficiency, hepatosplenomegaly, hernias, dysostosis multiplex, joint stiffness, and cognitive impairment.[4,5] MPS I is commonly classified as three separate entities, Hurler syndrome (severe form), Hurler-Scheie syndrome (intermediate form) and Scheie syndrome (mild form).[2-4] However, this classification system is based on disease severity and age of onset, not on any biochemical differences between the three syndromes.[5] All three forms of the disease are the result of the same enzymatic deficiency and represent varying degrees of severity along the disease continuum. The definitive diagnosis of MPS I is based on demonstrating deficient α-L-iduronidase activity in fibroblasts, leukocytes, plasma, or serum.[2,3,5]

Specific treatments for MPS I include hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy.[2,4,5] HSCT is indicated for the severe forms of MPS I, in children < 2 years of age who are cognitively intact.[2,4] HSCT has been shown to preserve intellectual development, reverse some aspects of somatic disease and increase survival.[2,4,5] Enzyme replacement therapy (Aldurazyme) does not cross the blood-brain barrier and is unlikely to improve cognitive or neurologic function.[2] Therefore, Aldurazyme is appropriate in children < 2 years of age who have already experienced cognitive decline, or who are cognitively intact with severe physical disease prior to HSCT to improve their health. Aldurazyme is also recommended in older patients with or without cognitive or neurologic decline.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Aldurazyme. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Aldurazyme as well as the monitoring required for adverse events and long-term efficacy, approval requires Aldurazyme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Aldurazyme is recommended in those who meet the following criteria:

FDA-Approved Indication

20. Mucopolysaccharidosis Type I (Hurler Syndrome, Hurler-Scheie Syndrome, and Scheie Syndrome). Approve for 1 year if the patient meets the following criteria (A and B):

A) The diagnosis is established by one of the following (i or ii):

i. Patient has a laboratory test demonstrating deficient α-L-iduronidase activity in leukocytes, fibroblasts, plasma, or serum; OR

ii. Patient has a molecular genetic test demonstrating α-L-iduronidase gene mutation; AND

B) Aldurazyme is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Aldurazyme is not recommended in the following situations:

56. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

263. Aldurazyme® intravenous infusion [prescribing information]. Novato, CA: Genzyme; December 2019.
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267. Martins AM, Dualibi AP, Norato D, et al. Guidelines for the management of mucopolysaccharidosis type I. *J Pediatr*. 2009;155(Suppl 2):S32-S46.

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Elaprase Prior Authorization Policy
- Elaprase® (idursulfase intravenous infusion – Shire Human Genetic Therapies)

REVIEW DATE: 04/12/2023

OVERVIEW

Elaprase, human iduronate-2-sulfatase (idursulfase), is indicated for patients with **Hunter syndrome** (**Mucopolysaccharidosis type II** [MPS II]).[1]

Disease Overview

MPS II or Hunter syndrome, is a rare, X-linked lysosomal storage disorder characterized by a deficiency of iduronate-2-sulfatase leading to the accumulation of glycosaminoglycans dermatan sulfate and heparin sulfate.[2,3] Males are almost exclusively affected, although there have been a few case reports of females with Hunter syndrome.[3,4] The onset, progression, and severity of MPS II is variable.[2-4] Most of the patients with MPS II have a severe form with neurologic involvement leading to cognitive impairment and neurologic regression.[3,4] Other manifestations of Hunter syndrome include course facial features, hepatosplenomegaly, cardiac and respiratory disease, short stature, and stiff joints and contractures.[2,3] The definitive diagnosis of MPS II is established by demonstrating deficient iduronate-2-sulfatase activity in leukocytes, fibroblasts, serum, or plasma; or mutations in the iduronate-2-sulfatase gene.[2,5] Definitive treatment of MPS II consists of enzyme replacement therapy with Elaprase.[2-4] Hematopoietic stem cell transplantation has not demonstrated clear neurological benefit to date and is not recommended for MPS II due to the high rate of morbidity and mortality associated with this therapy.[2,4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Elaprase. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Elaprase as well as the monitoring required for adverse events and long-term efficacy, approval requires Elaprase to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Elaprase is recommended in those who meet the following criteria:

FDA-Approved Indication

21. Mucopolysaccharidosis Type II (Hunter Syndrome). Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** The diagnosis is established by one of the following (i or ii):
  - **i.** Patient has a laboratory test demonstrating deficient iduronate-2-sulfatase activity in leukocytes, fibroblasts, serum, or plasma; OR
  - **ii.** Patient has a molecular genetic test demonstrating iduronate-2-sulfatase gene mutation; AND

B) Elaprase is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Elaprase is not recommended in the following situations:

57. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

268. Elaprase® intravenous infusion [prescribing information]. Lexington, MA: Shire Human Genetic Therapies; October 2021.
269. Scarpa M, Almassy Z, Beck M, et al. Mucopolysaccharidosis type II: European recommendations for the diagnosis and multidisciplinary management of a rare disease. *Orphanet J Rare Dis*. 2011;6:72.
270. Muenzer J, Beck M, Eng CM, et al. Multidisciplinary management of Hunter syndrome. *Pediatrics*. 2009;124:e1228-e1239.
271. Giugliani R, Federhen A, Munoz Rojas MV, et al. Mucopolysaccharidosis I, II, and VI: Brief review and guidelines for treatment. *Genet Mol Biol*. 2010;33:589-604.
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PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Elfabrio Prior Authorization Policy
- Elfabrio® (pegunigalsidase alfa intravenous infusion – Chiesi)

REVIEW DATE: 06/14/2023

OVERVIEW

Elfabrio, a PEGylated, crosslinked, chemically modified human alpha-galactosidase A (α-Gal A) enzyme, is indicated for the treatment of **Fabry disease** in adults.[1] The amino acid sequence of one subunit of Elfabrio consists of 405 amino acids, of which 398 amino acids are identical to human alpha-galactosidase A. Elfabrio catalyzes the breakdown of globotriaosylceramide (GL-3) and other α-galactyl-terminated neutral glycosphingolipids to ceramide and galactose and reduces the deposition of GL-3 in the capillary endothelium of the kidney and certain other cell types.

Disease Overview

Fabry disease is a rare inherited X-linked lysosomal storage disorder due to absent or significantly reduced α-Gal activity leading to the accumulation of GL-3 in a wide variety of cells throughout the body.[2-4] The accumulation of GL-3 leads to progressive multisystem disease, primarily impacting the kidney, heart, and nervous system.[3,4] Fabry disease can be divided into two phenotypes. A severe, classical phenotype that more commonly occurs in men without α-Gal activity, whereas a generally milder non-classical (late-onset) phenotype is found in men and women with some residual α-Gal activity.[2,3] Fabry disease is estimated to affect approximately 1 in 40,000 males and approximately 1 in 20,000 females. However, data from newborn screening programs suggest that the incidence of Fabry disease is generally underestimated and may equate to 1 per 3,100 live births, with late-onset phenotypes being more prevalent.[5] The diagnosis of Fabry disease can be confirmed in males by demonstrating a deficiency in α-Gal activity, and in all patients by identifying a Fabry disease causing gene mutation.[4] Long-term consequences of Fabry disease include hypertrophic cardiomyopathy, arrhythmias, renal failure, and stroke.[3] The kidney disease that occurs in Fabry disease is associated with progressive proteinuria and a decline in glomerular filtration rate, which over time, leads to end-stage renal disease requiring dialysis and ultimately, kidney transplantation.[2] Treatment with Elfabrio reduces the accumulation of GL-3 in the kidney (and in other organs), with the goal of stopping or slowing the decline in kidney function.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Elfabrio. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Elfabrio as well as the monitoring required for adverse events and long-term efficacy, approval requires Elfabrio to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Elfabrio is recommended in those who meet the following criteria:

FDA-Approved Indication

22. Fabry Disease. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** The patient is ≥ 18 years of age.
- **B)** The diagnosis is established by one of the following (i or ii):
  - **i.** Patient has a laboratory test demonstrating deficient α-galactosidase A activity in leukocytes or fibroblasts; OR
  - **ii.** Patient has a molecular genetic test demonstrating pathogenic mutations in the galactosidase alpha gene; AND
- **C)** Elfabrio is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Elfabrio is not recommended in the following situations:

58. Concurrent Use with Galafold (migalastat oral capsules). Galafold has not been evaluated for use in combination with Elfabrio. It is not FDA approved for concurrent use with enzyme replacement therapy.

59. Concurrent Use with Fabrazyme (agalsidase beta intravenous infusion).

60. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

273. Elfabrio® intravenous infusion [prescribing information]. Parma, Italy: Chiesi; May 2023.
274. Schiffmann R. Fabry Disease. *Handb Clin Neurol*. 2015;132:231-248.
275. Arends M, Wanner C, Hughes D, et al. Characterization of Classical and Nonclassical Fabry Disease: A Multinational Study. *J Am Soc Nephrol*. 2017;28:1631-1641.
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PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Fabrazyme Prior Authorization Policy
- Fabrazyme® (agalsidase intravenous infusion – Genzyme)

REVIEW DATE: 04/12/2023

OVERVIEW

Fabrazyme, a human α-galactosidase A (α-Gal), is indicated for use in patients with **Fabry disease**.[1] It is the same amino acid sequence as the native enzyme and is produced in Chinese hamster ovary cells via recombinant DNA technology. Fabrazyme catalyzes the breakdown of globotriaosylceramide (GL-3) and other α-galactyl-terminated neutral glycosphingolipids to ceramide and galactose and reduces the deposition of GL-3 in the capillary endothelium of the kidney and certain other cell types.

Disease Overview

Fabry disease is a rare inherited X-linked lysosomal storage disorder due to absent or significantly reduced α-Gal activity leading to the accumulation of GL-3 in a wide variety of cells throughout the body.[2-4] The accumulation of GL-3 leads to progressive multisystem disease, primarily impacting the kidney, heart and nervous system.[3,4] The incidence of Fabry disease is estimated to be about 1:117,000 live male births.[2] Fabry disease can be divided into two phenotypes. A severe, classical phenotype typically occurs in men without α-Gal activity, whereas a generally milder non-classical phenotype is found in men and women with some residual α-Gal activity.[2,3] The diagnosis of Fabry disease can be confirmed in males by demonstrating a deficiency in α-Gal activity, and in all patients by identifying a Fabry disease causing gene mutation.[4] Long-term consequences of Fabry disease include hypertrophic cardiomyopathy, arrhythmias, renal failure, and stroke.[3] The kidney disease that occurs in Fabry disease is associated with progressive proteinuria and a decline in glomerular filtration rate, which over time, leads to end-stage renal disease requiring dialysis and ultimately, kidney transplantation.[2] Treatment with Fabrazyme reduces the accumulation of GL-3 in the kidney (and in other organs), with the goal of stopping or slowing the decline in kidney function.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Fabrazyme. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Fabrazyme as well as the monitoring required for adverse events and long-term efficacy, approval requires Fabrazyme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Fabrazyme is recommended in those who meet the following criteria:

FDA-Approved Indication

23. Fabry Disease. Approve for 1 year if the patient meets the following criteria (A and B):

- **A)** The diagnosis is established by one of the following (i or ii):
  - **i.** Patient has a laboratory test demonstrating deficient α-galactosidase A activity in leukocytes or fibroblasts; OR
  - **ii.** Patient has a molecular genetic test demonstrating mutations in the galactosidase alpha gene; AND
- **B)** Fabrazyme is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Fabrazyme is not recommended in the following situations:

61. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

278. Fabrazyme® intravenous infusion [prescribing information]. Cambridge, MA: Genzyme; March 2021.
279. Schiffmann R. Fabry Disease. *Handb Clin Neurol*. 2015;132:231-248.
280. Arends M, Wanner C, Hughes D, et al. Characterization of Classical and Nonclassical Fabry Disease: A Multinational Study. *J Am Soc Nephrol*. 2017;28:1631-1641.
281. Laney DA, Bennett RL, Clarke V, et al. Fabry Disease Practice Guidelines: Recommendations of the National Society of Genetic Counselors. *J Genet Counsel*. 2013;22:555-564.

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Kanuma Prior Authorization Policy
- Kanuma® (sebelipase alfa intravenous infusion – Alexion)

REVIEW DATE: 04/12/2023

OVERVIEW

Kanuma, a human lysosomal acid lipase (LAL), indicated for the treatment of patients with a diagnosis of **LAL deficiency**.[1] It is produced in the egg white of genetically engineered chickens via recombinant DNA technology. LAL catalyzes the breakdown of cholesteryl esters to free cholesterol and fatty acids, and the breakdown of triglycerides to glycerol and free fatty acids.

Disease Overview

LAL deficiency is a rare lysosomal storage disorder characterized by absent or deficient LAL activity leading to the accumulation of cholesterol and triglycerides in the liver and other organs.[2,3] Patients with LAL deficiency often have dyslipidemias, cardiovascular disease and progressive liver disease.[2] The disorder has a heterogeneous presentation ranging from a rapidly progressive form occurring in infants which leads to death in the first year of life, to a childhood/adult-onset form with milder signs and symptoms. Almost all patients with childhood/adult-onset LAL deficiency have hepatomegaly with elevated liver transaminases and have an increased risk of developing fibrosis and cirrhosis.[3] The diagnosis of LAL deficiency is established by demonstrating deficient LAL activity in leukocytes, fibroblasts, or liver tissue; or by genetic testing.[2,3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Kanuma. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kanuma as well as the monitoring required for adverse events and long-term efficacy, approval requires Kanuma to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kanuma is recommended in those who meet the following criteria:

FDA-Approved Indication

24. Lysosomal Acid Lipase Deficiency. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** The diagnosis is established by one of the following (i or ii):
  - **i.** Patient has a laboratory test demonstrating deficient lysosomal acid lipase activity in leukocytes, fibroblasts, or liver tissue; OR
  - **ii.** Patient has a molecular genetic test demonstrating lysosomal acid lipase gene mutation; AND
- **B)** Kanuma is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kanuma is not recommended in the following situations:

62. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

282. Kanuma® intravenous infusion [prescribing information]. Cheshire, CT: Alexion; November 2021.
283. Reiner Z, Guardamagna O, Nair D, et al. Lysosomal acid lipase deficiency – an under-recognized cause of dyslipidaemia and liver dysfunction. *Atherosclerosis*. 2014;235:21-30.
284. Erwin AL. The role of sebelipase alfa in the treatment of lysosomal acid lipase deficiency. *Ther Adv Gastroenterol*. 2017;10:553-562.

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Lamzede Prior Authorization Policy
- Lamzede® (velmanase alfa-tycv intravenous infusion – Chiesi)

REVIEW DATE: 03/08/2023; selected revision 03/22/2023

OVERVIEW

Lamzede, a recombinant human lysosomal alpha-mannosidase, is indicated for the treatment of **non-central nervous system manifestations of alpha-mannosidosis** in adult and pediatric patients.[1]

Disease Overview

Alpha-mannosidosis is an ultra-rare autosomal recessive lysosomal storage disease. It is estimated to occur in 1-2:1,000,000 live births.[2] Alpha-mannosidosis results from reduced activity of the lysosomal enzyme, alpha-mannosidase, which is caused by gene variants in Mannosidase Alpha Class 2B Member 1 *(MAN2B1*). This results in accumulation of mannose-rich oligosaccharides in various tissues, which leads to significant and diverse multi-systemic manifestations, such as progressive motor function disturbances and physical disability, hearing and speech impairment, intellectual disability, and immune deficiency. Lamzede is the first and only enzyme replacement therapy approved for alpha-mannosidosis in the United States. There are no other therapies FDA approved for alpha-mannosidosis and treatment is targeted towards management of the various clinical manifestations of the disease. Hematopoietic stem cell transplantation (HSCT) has been used to prevent cognitive decline, preserve neurocognitive function, and prevent early death.[2-5] However, not all patients are eligible for HSCT and it is associated with risk of mortality and complications. Lamzede has been approved by the European Medicines Agency (EMA) in 2018. Diagnosis of alpha-mannosidosis is confirmed by molecular genetic testing and identification of biallelic pathogenic variants in *MAN2B1*. Alpha-mannosidase enzyme activity in peripheral blood leukocytes is 5% to 10% of normal activity in affected individuals.[6]

Clinical Efficacy

The efficacy of Lamzede in adult and pediatric patients with alpha-mannosidosis was established in two pivotal studies (rhLAMAN-05 and rhLAMAN-08) and one non-pivotal trial (rhLAMAN-10).[2-5] Patients with a confirmed diagnosis of alpha-mannosidosis, defined as alpha-mannosidase activity less than 10% of normal activity in blood leukocytes were enrolled. Lamzede demonstrated a statistically significant clearance of serum oligosaccharides vs. placebo in the pivotal trials. Lamzede also demonstrated improvement in endurance, pulmonary function, motor proficiency testing and a decrease in serum immunoglobulins.

Safety

Lamzede has a Boxed Warning for hypersensitivity reactions, including anaphylaxis.[1] Other Warnings/Precautions for Lamzede include infusion-associated reactions and embryofetal toxicity. Pretreatment with antihistamines, antipyretics, and/or corticosteroids should be considered to reduce the risk of hypersensitivity and infusion-related reactions.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lamzede. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lamzede as well as the monitoring required for adverse events and long-

term efficacy, approval requires Lamzede to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lamzede is recommended in those who meet the following criteria:

FDA-Approved Indication

25. Alpha-mannosidosis. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient has a confirmed diagnosis of alpha-mannosidosis, defined as alpha-mannosidase activity less than 10% of normal activity in blood leukocytes; AND
- **B)** Patient has biallelic pathogenic variants in Mannosidase Alpha Class 2B Member 1 (*MAN2B1)* as confirmed by mutation testing; AND
- **C)** Patient has non-central nervous system manifestations; AND
  Note: Examples of non-central nervous system manifestations include progressive motor function disturbances, physical disability, hearing and speech impairment, skeletal abnormalities, and immune deficiency.
- **D)** The medication is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lamzede is not recommended in the following situations:

63. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

285. Lamzede® intravenous infusion [prescribing information]. Cary, NC: Chiesi USA; February 2023.
286. Borgwardt L, Guffon N, Amraoui Y, et al. Efficacy and safety of velmanase alfa in the treatment of patients with alpha-mannosidosis: results from the core and extension phase analysis of a phase III multicentre, double-blind, randomised, placebo-controlled trial. *J Inherit Metab Dis*. 2018;41(6):1215-1223.
287. Data on file. Lamzede summary of studies evaluating safety and efficacy of velmanase alpha. Cheisi USA; received February 20, 2023.
288. Guffon N, Konstantopoulou V, Hennermann JB, et al. Long-term safety and efficacy of velmanase alpha (VA) treatment in children under 6 years of age with alpha-mannosidosis (AM). Presented at: 14th International Congress of Inborn Errors of Metabolism (ICIEM 2021); Sydney, Australia; November 21-23, 2021.
289. Lund A, Borgwardt L, Cattaneo F, et al. Comprehensive long-term efficacy and safety of recombinant human alpha-mannosidase (velmanase alfa) treatment in patients with alpha-mannosidosis. *J Inherit Metab Dis*. 2018;41:1225-1233.
290. Guffon N, Tylki-Szymanska A, Borgwardt L, et al. Recognition of alpha-mannosidosis in paediatric and adult patients: Presentation of a diagnostic algorithm from an international working group. *Mol Genet Metab*. 2019;126(4):470-474.

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Mepsevii Prior Authorization Policy
- Mepsevii® (vestronidase alfa-vjbk intravenous infusion – Ultragenyx)

REVIEW DATE: 04/12/2023

OVERVIEW

Mepsevii, a lysosomal beta glucuronidase (GUS), is indicated for the treatment of **Mucopolysaccharidosis type VII** ([MPS VII], Sly syndrome).[1] It is produced in a Chinese hamster ovary cell line via recombinant DNA technology. It has the same amino acid sequence as human GUS and catabolizes accumulated glycosaminoglycans in lysosomes in affected tissues.

Disease Overview

MPS VII or Sly syndrome is an extremely rare lysosomal storage disorder characterized by deficient GUS activity.[2] In MPS VII, the partially catabolized glycosaminoglycans, chondroitin sulfate, dermatan sulfate, and heparin sulfate accumulate in the lysosomes, ultimately leading to the signs and symptoms of the disease.[2,3] The onset, severity, and rate of progression of MPS VII is heterogeneous. Patients may present at birth with hydrops fetalis and only survive a few months while others may have milder disease and survive into their 40s.[2] However, most patients have mental retardation, hepatosplenomegaly, and musculoskeletal issues including short stature, course facial features, loss of range of motion, restricted mobility, scoliosis, and kyphosis. The diagnosis of MPS VII is established by demonstrating deficient GUS activity in leukocytes, fibroblasts, or serum; or by genetic testing.[3] Treatment for MPS VII includes enzyme replacement therapy with Mepsevii and hematopoietic stem cell transplantation.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Mepsevii. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Mepsevii as well as the monitoring required for adverse events and long-term efficacy, approval requires Mepsevii to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mepsevii is recommended in those who meet the following criteria:

FDA-Approved Indication

26. Mucopolysaccharidosis Type VII (Sly Syndrome). Approve for 1 year if the patient meets the following criteria (A and B):

- **A)** The diagnosis is established by one of the following (i or ii):
  - **i.** Patient has a laboratory test demonstrating deficient beta-glucuronidase activity in leukocytes, fibroblasts, or serum; OR
  - **ii.** Patient has a molecular genetic test demonstrating glucuronidase gene mutation; AND
- **B)** Mepsevii is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mepsevii is not recommended in the following situations:

64. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

291. Mepsevii® intravenous infusion [prescribing information]. Novato, CA: Ultragenyx; December 2020.
292. Montano AM, Lock-Hock N, Steiner RD, et al. Clinical course of sly syndrome (mucopolysaccharidosis type VII). *J Med Genet*. 2016;53:403-418.
293. Tomatsu S, Montano AM, Dung VC, et al. Mutations and polymorphisms in GUSB gene in mucopolysaccharidosis VII (Sly syndrome). *Hum Mutat*. 2009;30:511-519.

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Naglazyme Prior Authorization Policy
- Naglazyme® (galsulfase intravenous infusion – BioMarin)

REVIEW DATE: 04/12/2023

OVERVIEW

Naglazyme, a human *N*-acetylgalactosamine 4-sulfatase, is indicated for patients with **Mucopolysaccharidosis type VI** (Maroteaux – Lamy syndrome [MPS VI]).[1] It is produced in a Chinese hamster ovary cell line via recombinant DNA technology. The enzyme catalyzes the hydrolysis of the sulfate ester from the glycosaminoglycans, chondroitin 4-sulfate and dermatan sulfate. Naglazyme has been shown to improve walking and stair climbing capacity.

Disease Overview

MPS VI, or Maroteaux – Lamy syndrome, is a rare lysosomal storage disorder characterized by a deficiency of *N*-acetylgalactosamine 4-sulfatase (arylsulfatase B).[2,3] The enzyme deficiency results in the accumulation of partially hydrolyzed dermatan sulfate and chondroitin 4-sulfate in lysosomes leading to the signs and symptoms of the disease.[2,3] The onset, severity and rate of progression of MPS VI is heterogeneous; however, most patients are severely affected with a rapidly progressive form.[3] Clinical manifestations include course facial features, short stature, kyphoscoliosis, joint stiffness, pulmonary insufficiency, cardiac disease, hepatosplenomegaly, corneal clouding, and hernias.[2,3] The definitive diagnosis of MPS VI is established by demonstrating deficient arylsulfatase B enzyme activity in leukocytes or fibroblasts; or by genetic testing.[2,3] Definitive treatment of MPS VI consists of either enzyme replacement therapy with Naglazyme or hematopoietic stem cell transplantation. Due to the morbidity and mortality associated with hematopoietic stem cell transplantation, this therapy is typically reserved for patients who are intolerant of or do not respond to enzyme replacement therapy.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Naglazyme. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Naglazyme as well as the monitoring required for adverse events and long-term efficacy, approval requires Naglazyme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Naglazyme is recommended in those who meet the following criteria:

FDA-Approved Indication

27. Mucopolysaccharidosis Type VI (Maroteaux – Lamy Syndrome). Approve for 1 year if the patient meets the following criteria (A and B):

- **A)** The diagnosis is established by one of the following (i or ii):
  - **i.** Patient has a laboratory test demonstrating deficient *N*-acetylgalactosamine 4-sulfatase (arylsulfatase B) activity in leukocytes or fibroblasts; OR
  - **ii.** Patient has a molecular genetic test demonstrating arylsulfatase B gene mutation; AND
- **B)** Naglazyme is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Naglazyme is not recommended in the following situations:

65. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

294. Naglazyme® intravenous infusion [prescribing information]. Novato, CA: BioMarin; April 2020.
295. Harmatz PR, Shediac R. Mucopolysaccharidosis VI: Pathophysiology, diagnosis and treatment. *Front Biosci*. 2017;22:385-406.
296. Vairo F, Federhen A, Baldo G, et al. Diagnostic and treatment strategies in mucopolysaccharidosis VI. *Appl Clin Genet*. 2015;8:245-255.

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Revcovi Prior Authorization Policy
- Revcovi® (elapegademase-lvlr intramuscular injection – Chiesi)

REVIEW DATE: 12/13/2023

OVERVIEW

Revcovi, a recombinant adenosine deaminase, is indicated for the treatment of **adenosine deaminase severe combined immune deficiency (ADA-SCID)** in pediatric and adult patients.[1]

Disease Overview

ADA-SCID is an ultra-rare, autosomal recessive genetic disorder of purine metabolism affecting lymphocyte development, viability, and function.[1,2] It is estimated to occur in 1:200,000 to 1:1,000,000 live births. ADA is a purine salvage enzyme which metabolizes deoxyadenosine (dAdo) and adenosine (Ado) into deoxyinosine and inosine, respectively.[3] When ADA is deficient, dAdo accumulates in intracellular and extracellular compartments, along with its metabolite, deoxyadenosinetriphosphate (dATP). The buildup of both dAdo and dATP negatively impacts lymphocyte development and function by impeding DNA replication and repair, inducing apoptosis, and inhibiting lymphocyte activation.

There are a variety of phenotypes of ADA deficiency; ADA-SCID is the most severe and typically diagnosed before 1 year of age.[2] Infants with typical ADA-SCID have failure to thrive and opportunistic infections associated with marked depletion of B, T, and NK lymphocytes. Manifestations include persistent diarrhea, extensive dermatitis, recurrent pneumonia, and other life-threatening illnesses caused by opportunistic infections. Growth failure and other physical manifestations, including hepatic and neurologic abnormalities, may also be present. Without treatment, patients with ADA-SCID rarely survive beyond 1 to 2 years of age.

Guidelines

According to a consensus statement for management of ADA-SCID (2018) and updated guidelines in 2023, diagnosis is usually established by demonstrating absent or very low (< 1 % of normal) ADA catalytic activity, accompanied by elevated Ado or dAdo in plasma, urine, or dried blood spots.[3,4] This should be followed by genetic testing to confirm bi-allelic mutations in the *ADA* gene. Enzyme replacement therapy (ERT) is recommended by the consensus panel for all patients newly diagnosed with ADA-SCID as an immediate stabilizing measure. The ideal duration of ERT has not been established. The consensus recommends that most patients use ERT as a "bridge" for a few months to approximately 2 years, prior to undergoing curative therapy with a hematopoietic stem cell transplant (HSCT) or hematopoietic stem cell gene therapy. Long-term use of ERT has declined in the past 30 years and has not been systematically studied. Lymphocyte counts and function may deteriorate over time, contributing to increased risk of infections and malignancy. Therefore, ERT longer than 5 to 8 years should be avoided and employed on a continuous basis only when neither HSCT nor gene therapy have been available or effective. The consensus also suggests ERT use for patients with later-onset phenotypes who may not be ideal candidates for curative processes.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Revcovi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Revcovi, approval requires it to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Revcovi is recommended in those who meet the following criteria:

FDA-Approved Indication

3. Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID). Approve for 1 year if the patient meets the following (A and B):

- **A)** Patient has a diagnosis of ADA-SCID confirmed by one of the following (i or ii):
  - **i.** At baseline (i.e., prior to initiating enzyme replacement therapy), the patient has had absent or very low (< 1% of normal) adenosine deaminase (ADA) catalytic activity; OR
  - **ii.** Patient has had molecular genetic testing confirming bi-allelic mutations in the *ADA* gene; AND
- **B)** The medication is prescribed by or in consultation with an immunologist, hematologist/oncologist, or physician that specializes in ADA-SCID or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Revcovi is not recommended in the following situations:

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

40. Revcovi® [prescribing information]. Cary, NC: Chiesi; August 2022.
41. Hershfield M. GeneReviews [Internet]. Updated March 16, 2017. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1483/. Accessed on November 28, 2023.
42. Kohn DB, Hershfield MS, Puck JM, et al. Consensus approach for the management of severe combined immune deficiency caused by adenosine deaminase deficiency. *J Allergy Clin Immunol*. 2019;143(3):852-863.
43. Grunebaum E, Booth C, Cuvelier GDE, et al. Updated Management Guidelines for Adenosine Deaminase Deficiency. *J Allergy Clin Immunol Pract*. 2023 Jun;11(6):1665-1675.

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Strensiq Prior Authorization Policy
- Strensiq® (asfotase alfa subcutaneous injection – Alexion) **BB)**

REVIEW DATE: 07/26/2023

OVERVIEW

Strensiq, a tissue non-specific alkaline phosphatase (TNSALP), is indicated for the treatment of patients with **perinatal/infantile- and juvenile-onset hypophosphatasia** (HPP).[1] Strensiq is an enzyme replacement therapy which replaces human TNSALP.

Disease Overview

HPP is an inherited metabolic disease caused by a loss-of-function mutation in the gene which codes for TNSALP.[2] TNSALP is tissue-bound and expressed in high concentrations in the liver, kidney, neurons, neutrophils, bone, and teeth.[2,3] In HPP, inorganic pyrophosphate and pyridoxal 5'-phosphate, substrates for TNSALP, are increased and lead to disease manifestations. Inorganic pyrophosphate is an inhibitor of bone mineralization, and its accumulation leads to rickets and osteomalacia. Pyridoxal 5'-phosphate, a derivative of vitamin B_6, is necessary for the synthesis of gamma aminobutyric acid (GABA). However, for pyridoxal 5'-phosphate to enter the neuron, it must be dephosphorylated to allow pyridoxal to enter the neuron where it is rephosphorylated. The decreased synthesis of GABA in HPP leads to seizures.

HPP is a rare disease, with an estimated live-birth incidence, for the severe forms of HPP, of 1:100,000 in Canada and approximately 1:300,000 in Europe.[2,4] Prevalence in certain populations, such as Canadian Mennonites, may be as high as 1:2,500 births. Disease severity can range from neonatal death with almost no skeletal mineralization to dental problems in adults without any bone symptoms.[2-4] In patients most severely affected by HPP, mortality ranges from 50% to nearly 100% during infancy.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Strensiq. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Strensiq as well as the monitoring required for adverse events and long-term efficacy, approval requires Strensiq to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Strensiq is recommended in those who meet the following criteria:

FDA-Approved Indication

29. Hypophosphatasia – Perinatal/Infantile- and Juvenile-Onset. Approve for 1 year if the patient meets all of the following (A, B, C, and D):

12. Diagnosis is supported by one of the following (i, ii, or iii):

i. Molecular genetic testing documenting tissue non-specific alkaline phosphatase (*ALPL*) gene mutation; OR

ii. Low baseline serum alkaline phosphatase activity; OR

iii. An elevated level of a tissue non-specific alkaline phosphatase substrate (i.e., serum pyridoxal 5'-phosphate, serum or urinary inorganic pyrophosphate, urinary phosphoethanolamine); AND

13. Patient meets one of the following (i or ii):

i. Patient currently has, or has a history of, clinical manifestations consistent with hypophosphatasia; OR

Note: Examples of clinical manifestations include skeletal abnormalities, premature tooth loss, muscle weakness, poor feeding, failure to thrive, respiratory problems, vitamin B_6-dependent seizures.

ii. Patient has a family (parent or sibling) of hypophosphatasia without current clinical manifestations of hypophosphatasia; AND

14. Disease onset ≤ 18 years of age; AND

15. Strensiq is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of hypophosphatasia or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Strensiq is not recommended in the following situations:

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

97. Strensiq® subcutaneous injection [prescribing information]. Cheshire, CT: Alexion; April 2021.
98. Whyte MP. Hypophosphatasia: Enzyme Replacement Therapy Brings New Opportunities and New Challenges. *J Bone Miner Res.* 2017;32:667-675.
99. Orima H. Pathophysiology of Hypophosphatasia and the Potential Role of Asfotase Alfa. *Ther Clin Risk Manag.* 2016;12:777-786.
100. Millan JL, Plotkin H. Hypophosphatasia – Pathophysiology and Treatment. *Actual Osteol.* 2012;8:164-182.

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Sucraid Prior Authorization Policy
- Sucraid® (sacrosidase oral solution – QOL Medical)

REVIEW DATE: 04/12/2023

OVERVIEW

Sucraid, an enzyme replacement therapy, is indicated for the treatment of genetically determined sucrase deficiency, which is part of **congenital sucrase-isomaltase deficiency** (CSID).[1]

Disease Overview

CSID is an autosomal recessive intestinal disorder characterized by reduced or absent activity of the sucrase-isomaltase complex.[2,3] These enzymes are responsible for the hydrolysis of complex sugars and starches into simple sugars which are absorbed from the gastrointestinal tract. With absent or diminished enzyme activity, complex sugars and starches accumulate in the small intestine and lead to disease manifestations.[2] Symptoms include osmotic diarrhea, vomiting, bloating, abdominal pain, and steatorrhea.[2,3] Patients can occasionally experience dehydration, failure to thrive, developmental delay, and muscular hypotonia.[2] The diagnosis of CSID can be established by testing small intestine biopsy specimens for reduced or absent enzyme activity or by genetic testing to identify a mutation in the sucrase-isomaltase gene.[3,4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Sucraid. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sucraid as well as the monitoring required for adverse events and long-term efficacy, approval requires Sucraid to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sucraid is recommended in those who meet the following criteria:

FDA-Approved Indication

28. Congenital Sucrase-Isomaltase Deficiency. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** The diagnosis is established by one of the following (i or ii):
  - **i.** Patient has endoscopic biopsy of the small bowel with disaccharidase levels consistent with congenital sucrose-isomaltase deficiency as evidenced by ALL of the following (a, b, c, and d):
    - **a)** Decreased (usually absent) sucrase (normal reference: > 25 U/g protein); AND
    - **b)** Decreased to normal isomaltase (palatinase) [normal reference: > 5 U/g protein]; AND
    - **c)** Decreased maltase (normal reference: > 100 U/g protein); AND
    - **d)** Decreased to normal lactase (normal reference: > 15 U/g protein); OR

ii. Patient has a molecular genetic test demonstrating homozygous or compound heterozygous pathogenic or likely pathogenic sucrase-isomaltase gene variant; AND

B) Prior to starting therapy with Sucraid, patient had symptomatic congenital sucrose-isomaltase deficiency (e.g., diarrhea, bloating, abdominal cramping); AND

C) Sucraid is prescribed by or in consultation with a geneticist, gastroenterologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of congenital diarrheal disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sucraid is not recommended in the following situations:

66. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

297. Sucraid® oral solution [prescribing information]. Vero Beach, FL: QOL Medical; August 2021.
298. Naim HY, Heine M, Zimmer KP. Congenital sucrose-isomaltase deficiency: Heterogeneity of inheritance, trafficking, and function of an intestinal enzyme complex. *J Pediatr Gastroenterol Nutr*. 2012;55:S13-S20.
299. Cohen SA. The clinical consequences of sucrose-isomaltase deficiency. *Mol Cell Pediatr*. 2016;3:5.
300. Gericke B, Amiri M, Scott CR, Naim HY. Molecular pathogenicity of novel sucrose-isomaltase mutations found in congenital sucrose-isomaltase deficiency patients. *Biochim Biophys Acta Mol Basis Dis*. 2017;1863:817-826.

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Vimizim Prior Authorization Policy
- Vimizim® (elosulfase alfa intravenous infusion – BioMarin)

REVIEW DATE: 04/12/2023

OVERVIEW

Vimizim, a human *N*-acetylgalactosamine-6-sulfatase, is indicated for patients with **Mucopolysaccharidosis type IVA** (Morquio A syndrome [MPS IVA]).[1] It is produced in Chinese hamster ovary cells via recombinant DNA technology. Vimizim is a hydrolytic lysosomal enzyme which is taken up by lysosomes and hydrolyzes sulfate from the non-reduced ends of the glycosaminoglycans keratan sulfate and chondroitin-6-sulfate.

Disease Overview

MPS IVA (Morquio A syndrome) is a rare lysosomal storage disorder characterized by deficient *N*-acetylgalactosamine-6-sulfatase activity leading to the accumulation of chondroitin-6-sulfate and keratan sulfate in lysosomes in bone, cartilage, and ligaments.[2,3] The clinical course, onset, and severity of MPS IVA is heterogeneous.[2] Manifestations of MPS IVA include short trunk dwarfism with short neck, kyphoscoliosis, odontoid dysplasia, knock-knee, cervical spinal cord compression, hypermobile joints, cardiac disease, respiratory insufficiency, obstructive sleep apnea, corneal clouding, and dental abnormalities.[2-4] MPS IVA has not been associated with cognitive decline.[2] The definitive diagnosis of MPS IVA is established by demonstrating deficient *N*-acetylgalactosamine-6-sulfatase activity in leukocytes or fibroblasts; or by genetic testing.[2] Definitive treatment for MPS IVA consists of enzyme replacement therapy with Vimizim. Hematopoietic stem cell transplantation is not recommended for MPS IVA.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vimizim. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vimizim as well as the monitoring required for adverse events and long-term efficacy, approval requires Vimizim to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vimizim is recommended in those who meet the following criteria:

FDA-Approved Indication

29. Mucopolysaccharidosis Type IVA (Morquio A Syndrome). Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** The diagnosis is established by one of the following (i or ii):
  - **i.** Patient has a laboratory test demonstrating deficient *N*-acetylgalactosamine-6-sulfatase activity in leukocytes or fibroblasts; OR

ii. Patient has a molecular genetic test demonstrating *N*-acetylgalactosamine-6-sulfatase gene mutation; AND

B) Vimizim is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vimizim is not recommended in the following situations:

67. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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302. Akyol MU, et al. MPS Consensus Programme Co-Chairs. Recommendations for the management of MPS IVA: systematic evidence- and consensus-based guidance. *Orphanet J Rare Dis*. 2019 Jun 13;14(1):137.
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PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Xenpozyme Prior Authorization Policy
- Xenpozyme™ (olipudase alfa-rpcp intravenous infusion – Genzyme)

REVIEW DATE: 09/13/2023

OVERVIEW

Xenpozyme, a hydrolytic lysosomal sphingomyelin-specific enzyme, is indicated for the treatment of **non-central nervous system (CNS) manifestations of acid sphingomyelinase deficiency (ASMD)** in adult and pediatric patients.[1]

Disease Overview

ASMD is an autosomal recessive lysosomal storage disease that results from reduced activity of the enzyme acid sphingomyelinase (ASM), caused by pathogenic variants in the sphingomyelin phosphodiesterase 1 gene.[1,2] ASM degrades sphingomyelin to ceramide and phosphocholine.[1] The deficiency of ASM causes an intra-lysosomal accumulation of sphingomyelin (as well as cholesterol and other cell membrane lipids) in various tissues. Xenpozyme provides an exogenous source of ASM. Xenpozyme is not expected to cross the blood-brain barrier or modulate the CNS manifestations of ASMD.

ASMD has historically been known as Niemann-Pick disease type A and/or B and is associated with a spectrum of disease phenotypes.[2] ASMD type B (also known as chronic visceral ASMD or Niemann-Pick type B disease) and ASMD type A/B (chronic neurovisceral ASMD, Niemann-Pick disease type A/B, or intermediate phenotype) have disease onset from childhood to early adulthood. ASMD type B has minimal to no CNS involvement, while ASMB type A/B has less severe neurologic manifestations than those observed in ASMD type A, which is fatal in early childhood. Visceral manifestations in ASMD include interstitial lung disease with decreased diffusing capacity of the lung, hepatosplenomegaly, progressive liver disease with cirrhosis or fibrosis, dyslipidemia, osteopenia, and thrombocytopenia. The leading causes of early mortality in adults with ASMD are lung disease/infections, liver failure, and bleeding.

Clinical Efficacy

The efficacy of Xenpozyme in adults and pediatric patients with ASMD was established in two pivotal trials (ASCEND and ASCEND-PEDS, respectively).[2,3] The pivotal trials enrolled patients with ASMD types B or A/B, but not type A. Eligible patients also had splenomegaly (spleen volumes ≥ 5 multiples of normal [MN] in pediatric patients and ≥ 6 MN in adults). In adults and children, Xenpozyme treatment improved spleen and liver volume as well as diffusing capacity of the lungs for carbon monoxide.

Guidelines

A consensus guideline for ASMD diagnosis has been developed by an international expert panel.[4] When there is a suspicion of ASMD, an ASM enzyme assay should be performed followed by gene sequencing if the enzymatic test is indicative of ASMD. Whenever possible, an enzyme assay for ASM and glucocerebrosidase activity should be performed in parallel to distinguish ASMD from Gaucher disease. Gene sequencing can be conducted after diagnosis based on ASM activity, but is not diagnostic on its own because of the high number of genetic variants of unknown significance. Biomarkers, while useful in disease monitoring, should not be considered sufficient for ASMD diagnosis (i.e., these include plasma chitotriosidase, plasma lyso-sphingolipids, and oxysterols). Physicians should perform clinical assessments to predict the phenotype and clinical course of the disease upon identification of sphingomyelin phosphodiesterase-1 (SMPD1) pathogenic variants of unknown pathogenicity in pediatric patients.

Safety
Xenpozyme has a Boxed Warning for hypersensitivity reactions, including anaphylaxis.[1] Prior to administration, pretreatment with antihistamines, antipyretics, and/or corticosteroids should be considered and appropriate medical measures, including cardiopulmonary resuscitation equipment should be readily available during Xenpozyme administration.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Xenpozyme. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Xenpozyme as well as the monitoring required for adverse events and long-term efficacy, approval requires Xenpozyme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Xenpozyme is recommended in those who meet the following criteria:

FDA-Approved Indication

30. Acid Sphingomyelinase Deficiency (ASMD). Approve for 1 year if the patient meets the following (A, B, C, and D):
Note: ASMD has historically been known as Niemann-Pick Disease.
A) The diagnosis of ASMD meets ALL of the following (i, ii, and iii):
- **i.** The diagnosis of ASMD has been established by acid sphingomylinase (ASM) enzymatic assay testing; AND
- **ii.** The diagnosis of ASMD has been confirmed by mutation testing; AND
- **iii.** A diagnosis of Gaucher disease has been excluded; AND

B) Patient meets ONE of the following (i or ii):
- **i.** Patient has ASMD type B; OR
- **ii.** Patient has ASMD type A/B; AND

C) Patient has two or more non-central nervous system signs of ASMD type B or type A/B according to the prescriber; AND
Note: Examples of non-central nervous system signs of ASMD type B or type A/B include but are not limited to hepatosplenomegaly, interstitial lung disease, decreased diffusing capacity of the lungs, progressive liver disease with cirrhosis or fibrosis, dyslipidemia, osteopenia, thrombocytopenia, anemia, leukopenia.
D) The medication is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xenpozyme is not recommended in the following situations:

68. Acid Sphingomyelinase Deficiency (ASMD), Type A. Xenpozyme is indicated for non-central nervous system manifestations of ASMD. Xenpozyme is not expected to cross the blood-brain barrier or modulate the central nervous system manifestations of ASMD.[1] Patients with ASMD type A were excluded from the pivotal trials with Xenpozyme.[2,3]

69. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Erectile Dysfunction – Alprostadil Products Prior Authorization Policy
- Caverject® (alprostadil intracavernosal injection – Pfizer)
- Caverject Impulse® (alprostadil intracavernosal injection – Pfizer)
- Edex® (alprostadil intracavernosal injection – Endo)
- MUSE® (alprostadil urethral suppository – MEDA)

REVIEW DATE: 11/01/2023

OVERVIEW

All of the alprostadil products are indicated for the treatment of **erectile dysfunction** due to neurogenic, vasculogenic, psychogenic, or mixed etiology.[1-4] Additionally, intracavernosal Caverject may be used adjunct to other diagnostic tests in the diagnosis of erectile dysfunction.[1] Injectable alprostadil products include Caverject, Caverject Impulse (disposable, single-dose, dual chamber syringe system), and Edex.[1-3] MUSE is available as a single-use, medicated transurethral system for the delivery of alprostadil directly in the urethra.[4] MUSE is administered by inserting the applicator stem into the urethra after urination.[1]

These products have also been studied for penile rehabilitation.[5] Alprostadil may help the recovery of erectile function by promotion of cavernosal oxygenation levels. Several studies have demonstrated the efficacy of alprostadil injections and MUSE for early penile rehabilitation post radical prostatectomy.[6-12]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of alprostadil products. Intravenous (IV) or other routes of administration of alprostadil is not covered by this policy. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with alprostadil products as well as the monitoring required for adverse events and long-term efficacy, some approvals require alprostadil products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of alprostadil products are recommended in those who meet the following criteria:

FDA-Approved Indication

30. Erectile Dysfunction. Approve for 1 year.

Other Uses with Supportive Evidence

31. **Prophylaxis after Radical Prostatectomy (Early Penile Rehabilitation).** Approve for 1 year in treatment-naïve patients if they meet both of the following (A and B).
    A) Therapy will be started within 6 months of surgery; AND
    B) The medication is prescribed by or in consultation with an urologist

32. **Patient with a of Radical Prostatectomy who is Continuing Alprostadil Therapy (e.g., Edex, Caverject, MUSE).** Approve for 1 year if patient was started on therapy post-operatively and is currently continuing therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of alprostadil products are not recommended in the following situations:

8. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

216. Caverject® intracavernosal injection [prescribing information]. New York, NY: Pfizer; March 2023.
217. Caverject Impulse® intracavernosal injection [prescribing information]. New York, NY: Pfizer; December 2022.
218. Edex® intracavernosal injection [prescribing information]. Malvern, PA: Endo Pharmaceuticals, Inc.; July 2018.
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225. Raina R, Pahlajani G, Agarwal A, et al. The early use of transurethral alprostadil after radical prostatectomy potentially facilitates an earlier return of erectile function and successful sexual activity. *BJU Int.* 2007;100:1317-1321.
226. Raina R, Agarwal A, Ausmundson S, et al. Long-term efficacy and compliance of MUSE for erectile dysfunction following radical prostatectomy: SHIM (IIEF-5) analysis. *Int J Impot Res.* 2005;17:86-90.
227. Raina R, Nandipati KC, Agarwal A, et al. Combination therapy: Medicated urethral system for erection enhances sexual satisfaction in sildenafil citrate failure following nerve-sparing radical prostatectomy. *J Androl.* 2005;26:757-760.

CC) PRIOR AUTHORIZATION POLICY

13.

POLICY: Erectile Dysfunction – Sildenafil Prior Authorization Policy

- Viagra® (sildenafil tablets – Pfizer, generic)

REVIEW DATE: 11/01/2023

OVERVIEW

Sildenafil (Viagra, generic) are indicated for the treatment of **erectile dysfunction**.[1]

Sildenafil has been studied for other indications.

- **Benign Prostatic Hyperplasia.** The European Association of Urology guidelines (2022) note that phosphodiesterase type 5 inhibitors can be used in men with moderate-to-severe lower urinary tract symptoms with or without erectile dysfunction.[9] The guidelines add that based on the results from a meta-analysis[8], younger men with lower body mass index and more severe lower urinary tract symptoms benefit the most from phosphodiesterase type 5 inhibitors.
- **High-Altitude Pulmonary Edema.** Published guidelines for the prevention of high-altitude pulmonary edema recommend nifedipine as the preferred pharmacologic treatment option.[12] Other pharmacologic therapies include salmeterol, tadalafil, sildenafil, dexamethasone, or acetazolamide.
- **Prophylaxis after Radical Prostatectomy.** Viagra given on a daily basis has been used to improve the return of normal spontaneous erectile function, improve tissue oxygenation, and prevent penile fibrosis after nerve-sparing radical prostatectomy.[10,11] It is better to initiate a penile rehabilitation program as soon as possible after surgery in order to limit and prevent postoperative local hypoxygenation and fibrosis.
- **Pulmonary Arterial Hypertension**. Sildenafil tablets (Revatio®) are approved for pulmonary arterial hypertension.[2] Sildenafil (Viagra, generics) are available in 25 mg, 50 mg, and 100 mg tablets, and Revatio is available as 20 mg tablets. Viagra has been used for this diagnosis.[3,4] Doses of Viagra that were used in these reports ranged from 25 mg twice daily to 100 mg five times daily. Patients will have usually been started on Revatio 20 mg three times daily.
- **Raynaud's Phenomenon**. There are studies which show sildenafil has been beneficial in patients with Raynauds's phenomenon.[5,6] Guidelines from the European League against Rheumatism (EULAR) on the treatment of systemic sclerosis (2023) recommend considering dihydropyridine calcium channel blockers (CCBs), usually oral nifedipine, for first-line therapy of Raynaud's phenomenon in patients with systemic sclerosis.[7] Phosphodiesterase type 5 inhibitors should also be considered in such clinical scenarios.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of sildenafil. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with sildenafil as well as the monitoring required for adverse events and long-term efficacy, some approvals require sildenafil to be prescribed by or in consultation with a physician who specializes in the condition being treated.

228.

229. **Automation:** When available, the ICD-10 codes for male erectile dysfunction (ICD-10: N52.*) will be used for automation to allow approval of the requested medication. This automation is gender-selective and is not applicable for women; approval for use in women is always determined by prior authorization criteria.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of sildenafil is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Erectile Dysfunction**. Approve for 1 year.

Other Uses with Supportive Evidence

2. **Benign Prostatic Hyperplasia**. Approve for 1 year if the patient meets one of the following (A or B):
   Note: For men with erectile dysfunction and benign prostatic hyperplasia, use criterion 1 above.
   3. Patient has tried an alpha-1 (α1) blocker; OR
- Note: Examples of alpha-1 (α1) blockers include doxazosin, terazosin, tamsulosin, alfuzosin.
   4. Patient has tried a 5α-reductase inhibitor.
   Note: Examples of a 5α-reductase inhibitor includes finasteride, dutasteride.

5. **High-Altitude Pulmonary Edema (HAPE), Treatment or Prevention.** Approve for 1 year in patients who meet the following (A and B):
   A) Patient has HAPE or a of HAPE; AND
   B) Patient has tried one other pharmacologic therapy for the treatment or prevention of HAPE.
   Note: Examples of other pharmacologic therapy for the treatment of HAPE are nifedipine, Serevent (salmeterol inhalation powder), dexamethasone, acetazolamide, Cialis (tadalafil tablets).

6. **Prophylaxis After Radical Prostatectomy (Early Penile Rehabilitation).** Approve for 1 year in patients who meet the following (A and B):
   A) Patient had radical prostatectomy within the previous 12 months; AND
   B) The medication is prescribed by or in consultation with an urologist.

7. **Pulmonary Arterial Hypertension**. Approve for 1 year.

8. **Raynaud's Phenomenon**. Approve for 1 year if the patient meets one of the following (A or B):
   9. Patient has tried one calcium channel blocker; OR
- Note: Examples of calcium channel blockers include amlodipine, felodipine, nifedipine.
   B) According to the prescriber, use of a calcium channel blocker is contraindicated.
   Note: Examples of reasons a patient cannot take calcium channel blocker therapy include right heart failure or decreased cardiac output.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of sildenafil is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Viagra tablets [prescribing information]. New York, NY: Pfizer; December 2017.
2. Revatio® tablets [prescribing information]. New York, NY: Pfizer; January 2023.
3. Garg N, Sharma MK, Sinha N. Role of oral sildenafil in severe pulmonary arterial hypertension: Clinical efficacy and dose response relationship. *Int J Cardiol.* 2007;120:306-313.
4. Galié N, Ghofrani HA, Torbicki A, et al; Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med.* 2005;353:2148-2157.
5. Fernandez-Codina A, Canas-Ruano E, Pope JE. Management of Raynaud's phenomenon in systemic sclerosis-a practical approach. *J Scleroderm Relat Disord*. 2019;4(2):102-110.
6. Hinze AM, Wigley FM. Pharmacotherapy options in the management of Raynaud's phenomenon. *Curr Treat Opt Rheumatol.* 2018;4(3):235-254.
7. Del Galdo F, Lescoat A, Conaghan PG, et al. 2023 Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis. 2023;82:154-155.
8. Gacci M, Corona G, Salvi M, et al. A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with α-blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. *Eur. Urol.* 2012;61:994-1003.
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PRIOR AUTHORIZATION POLICY

POLICY: Erectile Dysfunction – Stendra Prior Authorization Policy
- Stendra™ (avanafil tablets – Mist Pharmaceuticals)

REVIEW DATE: 11/01/2023

OVERVIEW
Stendra is a phosphodiesterase type 5 (PDE5) inhibitor indicated for the treatment of **erectile dysfunction**.[1]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Stendra. All approvals are provided for the duration noted below.

Automation: When available, the ICD-10 codes for male erectile dysfunction (ICD-10: N52.*) will be used for automation to allow approval of the requested medication. This automation is gender-selective and is not applicable for women; approval for use in women is always determined by prior authorization criteria.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Stendra is recommended in those who meet the following criteria:

FDA-Approved Indications

10. Erectile Dysfunction. Approve for 1 year.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Stendra is not recommended in the following situations:

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES
230. Stendra™ tablets [prescribing information]. Cranford, NJ: Mist Pharmaceuticals; October 2022.

DD) PRIOR AUTHORIZATION POLICY

14.

POLICY: Erectile Dysfunction – Tadalafil Prior Authorization Policy
- Cialis® (tadalafil tablets – Eli Lilly, generics)

REVIEW DATE: 11/01/2023

OVERVIEW

Tadalafil (Cialis, generics) is indicated for the following uses[1]:
- **Benign prostatic hyperplasia**.
- **Erectile dysfunction**.
- **Erectile dysfunction and the signs and symptoms of benign prostatic hyperplasia**.

Tadalafil has been studied for other indications:
- **High-Altitude pulmonary edema.** Published guidelines for the prevention of high-altitude pulmonary edema recommend nifedipine as the preferred pharmacologic treatment option.[11] Other pharmacologic therapies include salmeterol, sildenafil, dexamethasone, or acetazolamide.
- **Prophylaxis after radical prostatectomy.** Multiple studies have evaluated the efficacy of tadalafil for prophylaxis after radical prostatectomy.[5-7]
- **Pulmonary arterial hypertension.** Adcirca® (tadalafil tablets, generic) contain the same active ingredient as tadalafil (Cialis, generic) and is indicated for the treatment of pulmonary arterial hypertension. Tadalafil (Cialis, generic) is available in 2.5 mg, 5 mg, 10 mg, and 20 mg tablets. Adcirca is available as a 20 mg tablet. Tadalafil (Cialis, generic) has been used in multiple studies for pulmonary arterial hypertension.[8-10]
- **Raynaud's phenomenon.** There are studies which show tadalafil has been beneficial in patients with Raynaud's phenomenon.[2,3] Guidelines from the European League against Rheumatism (EULAR) on the treatment of systemic sclerosis (2023) recommend considering dihydropyridine calcium channel blockers (CCBs), usually oral nifedipine, for first-line therapy of Raynaud's phenomenon in patients with systemic sclerosis.[4] Phosphodiesterase type 5 inhibitors should also be considered in such clinical scenarios.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of tadalafil. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with tadalafil as well as the monitoring required for adverse events and long-term efficacy, some approvals require tadalafil to be prescribed by or in consultation with a physician who specializes in the condition being treated.

A) **<u>Automation</u>:** When available, the ICD-10 codes for male erectile dysfunction (ICD-10: N52.*) will be used for automation to allow approval of the requested medication. This automation is gender-selective and is not applicable for women; approval for use in women is always determined by prior authorization criteria.

B)

C)

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of tadalafil is recommended in those who meet one of the following criteria:

FDA-Approved Indications

11. Benign Prostatic Hyperplasia. Approve for 1 year if the patient meets one of the following (A or B):
Note: For men with erectile dysfunction and benign prostatic hyperplasia, use criterion 2 below.
D) Patient has tried an alpha-1 (α1) blocker; OR
1. Note: Examples of alpha-1 (α1) blockers include doxazosin, terazosin, tamsulosin, alfuzosin.
B) Patient has tried a 5α-reductase inhibitor.
Note: Examples of 5α-reductase inhibitor includes finasteride, dutasteride.

12. Erectile Dysfunction. Approve for 1 year.

Other Uses with Supportive Evidence

13. High-Altitude Pulmonary Edema (HAPE), Treatment or Prevention. Approve for 1 year in patients who meet the following (A and B):
A) Patient has HAPE or a of HAPE; AND
B) Patient has tried one other pharmacologic therapy for treatment or prevention of HAPE.
Note: Examples of other pharmacologic therapy for the treatment of HAPE are nifedipine, Serevent (salmeterol inhalation powder), dexamethasone, acetazolamide, sildenafil.

14. Prophylaxis After Radical Prostatectomy (Early Penile Rehabilitation). Approve for 1 year in patients who meet the following (A and B):
A) Patient had radical prostatectomy within the previous 12 months; AND
B) The medication is prescribed by or in consultation with an urologist.

15. Pulmonary Arterial Hypertension (PAH). Approve for 1 year in patients who cannot use Adcirca (tadalafil tablets, generic) because the dose is not available using Adcirca (tadalafil tablets, generic), that is, patients who are using 10 mg doses of tadalafil (Cialis, generic).
Note: Patients using 20 mg or 40 mg of tadalafil (Cialis, generic) for PAH should use Adcirca (tadalafil tablets, generic).

16. Raynaud's Phenomenon. Approve for 1 year if the patient meets one of the following (A or B):
A) Patient has tried one calcium channel blocker; OR
2. Note: Examples of calcium channel blockers include amlodipine, felodipine, nifedipine.
B) According to the prescriber, use of a calcium channel blocker is contraindicated.
Note: Examples of reasons a patient cannot take calcium channel blocker therapy include right heart failure or decreased cardiac output.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of tadalafil is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

3. Cialis® tablets [prescribing information]. Indianapolis, IN: Eli Lilly; April 2023.
4. Fernandez-Codina A, Canas-Ruano E, Pope JE. Management of Raynaud's phenomenon in systemic sclerosis-a practical approach. *J Scleroderm Relat Disord*. 2019;4(2):102-110.

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• PRIOR AUTHORIZATION POLICY

POLICY: Erectile Dysfunction – Vardenafil Prior Authorization Policy
- Levitra® (vardenafil tablets – GlaxoSmithKline, generic)
- Staxyn™ (vardenafil orally disintegrating tablet – GlaxoSmithKline, generic)

REVIEW DATE: 11/01/2023

OVERVIEW

Vardenafil (Levitra, generic) and vardenafil orally disintegrating tablets (Staxyn, generic) are indicated for the treatment of **erectile dysfunction**.[1,2]

Vardenafil has been studied for other indications:

- **Benign Prostatic Hyperplasia.** Vardenafil has been studied in benign prostatic hyperplasia.[5,6] The European Association of Urology guidelines (2022) note that phosphodiesterase type 5 inhibitors can be used in men with moderate-to-severe lower urinary tract symptoms with or without erectile dysfunction.[7] The guidelines add that based on the results from a meta-analysis[8], younger men with lower body mass index and more severe lower urinary tract symptoms benefits the most from phosphodiesterase type 5 inhibitors.
- **Prophylaxis after Radical Prostatectomy.** Vardenafil was studied in men following bilateral nerve-sparing radical prostatectomy.[9]
- **Raynaud's Phenomenon.** Vardenafil has been studied in patients with Raynaud's phenomenon.[3,4] Vardenafil improved digital blood flow and decreased the number of Raynaud's attacks. Guidelines from the European League against Rheumatism (EULAR) on the treatment of systemic sclerosis (2023) recommend considering dihydropyridine calcium channel blockers (CCBs), usually oral nifedipine, for first-line therapy of Raynaud's phenomenon in patients with systemic sclerosis.[10] Phosphodiesterase type 5 inhibitors should also be considered in such clinical scenarios.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of vardenafil tablets and vardenafil orally disintegrating tablets. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with vardenafil as well as the monitoring required for adverse events and long-term efficacy, some approvals require vardenafil to be prescribed by or in consultation with a physician who specializes in the condition being treated.

- **Automation:** When available, the ICD-10 codes for male erectile dysfunction (ICD-10: N52.*) will be used for automation to allow approval of the requested medication. This automation is gender-selective and is not applicable for women; approval for use in women is always determined by prior authorization criteria.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of vardenafil is recommended in those who meet one of the following criteria:

FDA-Approved Indications

17. Erectile Dysfunction. Approve for 1 year.

Other Uses with Supportive Evidence

18. Benign Prostatic Hyperplasia. Approve for 1 year if the patient meets one of the following (A or B):
- Note: For men with erectile dysfunction and benign prostatic hyperplasia, use criterion 1 above.

A) Patient has tried an alpha-1 (α1) blocker; OR
Note: Examples of alpha-1 (α1) blockers include doxazosin, terazosin, tamsulosin, alfuzosin.

B) Patient has tried a 5α-reductase inhibitor.
Note: Examples of 5α-reductase inhibitor includes finasteride, dutasteride.

19. Prophylaxis After Radical Prostatectomy (Early Penile Rehabilitation). Approve for 1 year in patients who meet the following (A and B):
- **A)** Patient had radical prostatectomy within the previous 12 months; AND
- **B)** The medication is prescribed by or in consultation with an urologist.
-

20. Raynaud's Phenomenon. Approve for 1 year if the patient meets one of the following (A or B):
- **A)** Patient has tried one calcium channel blocker; OR
- Note: Examples of calcium channel blockers include amlodipine, felodipine, nifedipine.
- **B)** According to the prescriber, use of a calcium channel blocker is contraindicated.
- Note: Examples of reasons a patient cannot take calcium channel blocker therapy include right heart failure or decreased cardiac output.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of vardenafil is not recommended in the following situations:
-

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Erythropoiesis-Stimulating Agents – Aranesp Prior Authorization Policy
- Aranesp® (darbepoetin alfa intravenous or subcutaneous injection – Amgen)

REVIEW DATE: 07/19/2023

OVERVIEW

Aranesp, an erythropoiesis-stimulating agent (ESA), is indicated for the following uses:[1]

- **Anemia due to chronic kidney disease** (CKD), including patients on dialysis and patients not on dialysis.
- **Anemia due to chemotherapy in patients with cancer,** in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

Aranesp has not been shown to improve quality of life, fatigue, or patient well-being.[1] Aranesp is not indicated for the following uses:

- In patients with cancer receiving hormonal agents, biologic products, or radiotherapy unless also receiving concomitant myelosuppressive chemotherapy.
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- In patients with cancer receiving myelosuppressive chemotherapy in whom anemia can be managed by transfusion.
- As a substitute for red blood cell (RBC) transfusions in those who require immediate correction of anemia.

Therapy should be initiated for **adults with CKD on dialysis** when the hemoglobin (Hb) level is < 10.0 g/dL and if the Hb level approaches or exceeds 11.0 g/dL, reduce or interrupt the Aranesp dose.[1] For **adults with CKD not on dialysis**, consider initiating Aranesp only when Hb is < 10.0 g/dL and other considerations apply (e.g., rate of Hb decline indicates patient is likely to need RBC transfusion and reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal). If the Hb level exceeds 10.0 g/dL, reduce or interrupt the Aranesp dose and use the lowest dose sufficient to reduce the need for RBC transfusions. For **pediatric patients with CKD**, initiate Aranesp when the Hb < 10.0 g/dL and if the Hb level approaches 12.0 g/dL, reduce or interrupt the dose of Aranesp. Initiate Aranesp for **patients on cancer chemotherapy** only if the Hb is < 10.0 g/dL and if there is a minimum of two additional months of planned chemotherapy. Use the lowest dose of Aranesp to avoid RBC transfusions.

Guidelines

The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for anemia in CKD (2012) state that for adults with CKD on dialysis, ESA therapy should be used to avoid having the Hb concentration fall below 9.0 g/dL by initiating ESA therapy when the Hb is between 9.0 and 10.0 g/dL.[2] The guidelines recommend against ESA therapy for adult patients with CKD who are not on dialysis when Hb levels are ≥ 10.0 g/dL. For adult patients with CKD who are not on dialysis with Hb levels < 10.0 g/dL, the decision whether to initiate ESA therapy should be individualized based on many factors (e.g., prior response to iron therapy, the risk of needing a transfusion, presence of symptoms). In general, ESAs should not be used to maintain Hb concentrations above 11.5 g/dL in adult patients with CKD. For pediatric patients with CKD, the Hb concentration in which ESAs should be initiated in the individual patient should be considered while being aware of the potential benefits and potential harms. In all pediatric patients with

CKD receiving ESA therapy, the selected Hb concentration should be in the range of 11.0 to 12.0 g/dL. Iron supplementation can improve response to ESA therapy. Baseline and periodic monitoring (e.g., iron, total iron-binding capacity, transferrin saturation, or ferritin levels) and instituting iron replacement when needed may be useful in limiting the need for ESAs, maximizing symptomatic improvement in patients, and determining the reason for inadequate response to ESAs. Iron deficiency can occur following continued ESA use. Therefore, iron supplementation is required in most patients to maintain an optimal response.

Aranesp is recommended in several guidelines from the National Comprehensive Cancer Network (NCCN):

- **Myelodysplastic Syndrome (MDS):** NCCN guidelines (version 1.2023 – September 12, 2022) list Aranesp and epoetin alfa products as having utility in anemic, symptomatic patients with MDS if serum erythropoietin levels are ≤ 500 mU/mL.[3] Iron stores should be adequate. Due to safety issues, the guidelines suggest that ESAs be used in the management of symptomatic anemia in patients with MDS and to aim for a target Hb range of 10 to 12.0 g/dL but not to exceed 12.0 g/dL.
- **Myeloproliferative Neoplasms:** The NCCN guidelines (version 1.2023 – May 19, 2023) address Aranesp and epoetin alfa products as options for treatment of patients with anemia related to myelofibrosis having a serum erythropoietin level < 500 mU/mL.[4] Iron stores should be adequate. The guidelines also advise that ESAs are not effective for the management of transfusion-dependent anemia.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Aranesp in patients with conditions other than CKD who are on dialysis. The intent of this policy is to provide recommendations for uses other than anemia in patients with CKD who are on dialysis. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Aranesp as well as the monitoring required for adverse events and long-term efficacy, approval requires Aranesp to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Aranesp is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Anemia in a Patient with Chronic Kidney Disease who is on Dialysis.** Approve for 3 years.

2. **Anemia in a Patient with Chronic Kidney Disease who is not on Dialysis.** Approve for 1 year if the patient meets the following (A or B):
   A) Initial Therapy. Approve if the patient meets the following (i and ii):
   i. Patient meets one of the following (a or b):
      a) Patient is ≥ 18 years of age with a hemoglobin < 10.0 g/dL; OR
      b) Patient is < 18 years of age with a hemoglobin ≤ 11.0 g/dL; AND
   ii. Patient meets one of the following (a or b):
      a) Patient is currently receiving iron therapy; OR
      b) Patient has adequate iron stores according to the prescriber; OR

B) Patient is Currently Receiving an Erythropoiesis-Stimulating Agent. Approve if the patient meets the following (i and ii):
Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit), a darbepoetin alfa product (e.g., Aranesp), or a methoxy polyethylene glycol-epoetin beta product (e.g., Mircera).

i. Patient has a hemoglobin ≤ 12.0 g/dL; AND

ii. Patient meets one of the following (a or b):

a) Patient is currently receiving iron therapy; OR

b) Patient has adequate iron stores according to the prescriber.

3. Anemia in a Patient with Cancer due to Cancer Chemotherapy. Approve for 6 months if the patient meets the following (A or B):

A) Initial Therapy. Approve if the patient meets the following (i, ii, and iii):

i. Patient has a hemoglobin < 10.0 g/dL; AND

ii. Patient meets BOTH of the following (a and b):

a) Patient is currently receiving myelosuppressive chemotherapy; AND

b) According to the prescriber, myelosuppressive chemotherapy is considered non-curative; AND

iii. Patient meets one of the following (a or b):

a) Patient is currently receiving iron therapy; OR

b) Patient has adequate iron stores according to the prescriber; OR

B) Patient is Currently Receiving an Erythropoiesis-Stimulating Agent. Approve if the patient meets the following (i, ii, and iii):
Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit) or a darbepoetin alfa product (e.g., Aranesp).

i. Patient has a hemoglobin ≤ 12.0 g/dL; AND

ii. Patient meets BOTH of the following (a and b):

a) Patient is currently receiving myelosuppressive chemotherapy; AND

b) According to the prescriber, myelosuppressive chemotherapy is considered non-curative; AND

iii. Patient meets one of the following (a or b):

a) Patient is currently receiving iron therapy; OR

b) Patient has adequate iron stores according to the prescriber.

Other Uses with Supportive Evidence

4. Anemia Associated with Myelodysplastic Syndrome. Approve for 1 year if the patient meets the following (A or B):

A) Initial Therapy. Approve if the patient meets the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets one of the following (a or b):

a) Patient has a hemoglobin < 10.0 g/dL; OR

b) Patient has a serum erythropoietin level ≤ 500 mU/mL; AND

iii. Patient meets one of the following (a or b):

a) Patient is currently receiving iron therapy; OR

b) Patient has adequate iron stores according to the prescriber; AND

iv. The medication is prescribed by or in consultation with a hematologist or oncologist.

B) Patient is Currently Receiving an Erythropoiesis-Stimulating Agent. Approve if the patient meets the following (i, ii, iii, and iv):

Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit) or a darbepoetin alfa product (e.g., Aranesp).

i. Patient is ≥ 18 years of age; AND
ii. Patient has a hemoglobin ≤ 12.0 g/dL; AND
iii. Patient meets one of the following (a or b):
  a) Patient is currently receiving iron therapy; OR
  b) Patient has adequate iron stores according to the prescriber; AND
iv. The medication is prescribed by or in consultation with a hematologist or oncologist.

5. **Anemia Associated with Myelofibrosis.** Approve for the duration noted below if the patient meets the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following (i, ii, and iii):
  i. Patient meets one of the following (a or b):
    a) Patient has a hemoglobin < 10.0 g/dL; OR
    b) Patient has a serum erythropoietin level ≤ 500 mU/mL; AND
  ii. Patient meets one of the following (a or b):
    a) Patient is currently receiving iron therapy; OR
    b) Patient has adequate iron stores according to the prescriber; AND
  iii. The medication is prescribed by or in consultation with a hematologist or oncologist.

B) Patient is Currently Receiving an Erythropoiesis-Stimulating Agent. Approve for 1 year if the patient meets the following (i, ii, iii, and iv):
  Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit) or a darbepoetin alfa product (e.g., Aranesp).
  i. Patient has a hemoglobin ≤ 12.0 g/dL; AND
  ii. Patient meets one of the following (a or b):
    a) Patient is currently receiving iron therapy; OR
    b) Patient has adequate iron stores according to the prescriber; AND
  iii. According to the prescriber, patient has responded to therapy defined as hemoglobin ≥ 10 g/dL or a hemoglobin increase of ≥ 2 g/dL; AND
  iv. The medication is prescribed by or in consultation with a hematologist or oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Aranesp is not recommended in the following situations:

1. **Anemia Associated with Cancer in a Patient not Receiving Myelosuppressive Cancer Chemotherapy.** Aranesp is not indicated in patients with cancer who are not receiving cancer chemotherapy.[1]

2. **Anemia Associated with Acute Myelogenous Leukemias (AML), Chronic Myelogenous Leukemias (CML) or other Myeloid Cancers.** Aranesp is indicated for use in non-myeloid cancers. AML and CML are examples of myeloid cancers.[1]

3. **Anemia Associated with Radiotherapy in Cancer.** Aranesp is not indicated for use in patients with cancer who are given only radiation therapy.[1]

4. **To Enhance Athletic Performance.** Aranesp is not recommended for approval because this indication is excluded from coverage in a typical pharmacy benefit.

5. **Anemia due to Acute Blood Loss.** Use of Aranesp is not appropriate in these types of situations.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Erythropoiesis-Stimulating Agents – Epoetin Alfa Products Prior Authorization Policy
- Epogen® (epoetin alfa intravenous or subcutaneous injection – Amgen)
- Procrit® (epoetin alfa intravenous or subcutaneous injection – Janssen)
- Retacrit® (epoetin alfa-epbx intravenous or subcutaneous injection – Pfizer/Hospira)

REVIEW DATE: 06/28/2023

OVERVIEW

Epoetin alfa (Epogen, Procrit, Retacrit), an erythropoiesis-stimulating agent (ESA), is indicated for the following uses:[1-3]

- **Anemia due to chronic kidney disease** (CKD), including patients on dialysis and patients not on dialysis to decrease the need for red blood cell (RBC) transfusions.
- **Anemia due to chemotherapy in patients with cancer**, in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.
- **Anemia due to zidovudine**, in patients with human immunodeficiency virus (HIV) infection.
- **Reduction of allogeneic RBC transfusions**, in patients with perioperative hemoglobin (Hb) > 10.0 to ≤ 13.0 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery.

Epoetin alfa has not been shown to improve quality of life, fatigue, or patient well-being.[1-3] Epoetin alfa is not indicated for the following uses:

- Patients with cancer receiving hormonal agents, biologic products, or radiotherapy unless also receiving concomitant myelosuppressive chemotherapy.
- Patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- Patients with cancer receiving myelosuppressive chemotherapy in whom anemia can be managed by transfusion.
- Patients scheduled for surgery who are willing to donate autologous blood.
- Patients undergoing cardiac or vascular surgery.
- As a substitute for RBC transfusions in those who require immediate correction of anemia.

Therapy should be initiated for patients with CKD on dialysis when the Hb level is < 10.0 g/dL and if the Hb level approaches or exceeds 11.0 g/dL, reduce or interrupt the dose of epoetin alfa.[1-3] For adults with CKD who are not on dialysis, epoetin alfa should be initiated when the Hb is < 10.0 g/dL and other considerations apply (e.g., patient is likely to need transfusions). If the Hb exceeds 10.0 g/dL, reduce or interrupt the epoetin alfa dose and use the lowest dose sufficient to reduce the need for RBC transfusions. Epoetin alfa is indicated for the treatment of anemia due to zidovudine given at ≤ 4,200 mg per week in HIV-infected patients with endogenous serum erythropoietin levels of ≤ 500 mU/mL. It is recommended to withhold epoetin alfa if Hb exceeds 12.0 g/dL. Data show that epoetin alfa elevated or maintained Hb and/or hematocrit and decreased transfusions in anemic patients (Hb < 10.0 g/dL) who were receiving zidovudine. Patients with baseline endogenous serum erythropoietin levels ≤ 500 mU/mL derived greater benefit with epoetin alfa (e.g., achievement of higher hematocrit, reduction in transfusion requirements) compared with those having levels greater than this threshold. Initiate epoetin alfa for patients on cancer chemotherapy only if the Hb is < 10.0 g/dL. Use the lowest dose of epoetin alfa necessary to avoid RBC

transfusions. Hb can be increased to (or near) a concentration of 12.0 g/dL at which time the dose of epoetin alfa should be titrated to maintain that level.

Guidelines

The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for anemia in CKD (2012) state that for adults with CKD on dialysis ESA therapy should be used to avoid having the Hb concentration fall below 9.0 g/dL by initiating ESA therapy when the Hb is between 9.0 and 10.0 g/dL.[4] The guidelines recommend against ESA therapy for adult patients with CKD who are not on dialysis when Hb levels are ≥ 10.0 g/dL. For adult patients with CKD who are not on dialysis with Hb levels < 10.0 g/dL, the decision whether to initiate ESA therapy should be individualized based on many factors (e.g., prior response to iron therapy, the risk of needing a transfusion, presence of symptoms). In general, ESAs should not be used to maintain Hb concentrations above 11.5 g/dL in adult patients with CKD. For pediatric patients with CKD, the Hb concentration in which ESAs should be initiated in the individual patient should be considered while being aware of the potential benefits and potential harms. In all pediatric patients with CKD receiving ESA therapy, the selected Hb concentration should be in the range of 11.0 to 12.0 g/dL. Iron supplementation can improve response to ESA therapy. Baseline and periodic monitoring (e.g., iron, total iron-binding capacity, transferrin saturation, or ferritin levels) and instituting iron replacement when needed may be useful in limiting the need for ESAs, maximizing symptomatic improvement in patients, and determining the reason for inadequate response to ESAs. Iron deficiency can occur following continued ESA use. Therefore, iron supplementation is required in most patients to maintain an optimal response.

Epoetin alfa is recommended in guidelines from the National Comprehensive Cancer Network (NCCN):

- **Myelodysplastic Syndrome (MDS):** NCCN guidelines (version 1.2023 – September 12, 2022) list Aranesp and epoetin alfa products as having utility in anemic, symptomatic patients with MDS if serum erythropoietin levels are ≤ 500 mU/mL.[5] Iron stores should be adequate. Due to safety issues, the guidelines suggest that ESAs be used in the management of symptomatic anemia in patients with MDS and to aim for a target Hb range of 10 to 12.0 g/dL but not to exceed 12.0 g/dL.
- **Myeloproliferative Neoplasms:** The NCCN guidelines (version 1.2023 – May 19, 2023) address Aranesp and epoetin alfa products as options for treatment of patients with anemia related to myelofibrosis having a serum erythropoietin level ≤ 500 mU/mL.[6] Iron stores should be adequate. The guidelines also advise that ESAs are not effective for the management of transfusion-dependent anemia.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of epoetin alfa products in patients with conditions other than CKD who are on dialysis. The intent of this policy is to provide recommendations for uses other than anemia in patients with CKD who are on dialysis. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with epoetin alfa as well as the monitoring required for adverse events and long-term efficacy, approval requires epoetin alfa to be prescribed by or in consultation with a physician who specializes in the condition being treated in some circumstances.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of epoetin alfa is recommended in those who meet one of the following criteria:

FDA-Approved Indications

4. **Anemia in a Patient with Chronic Kidney Disease who is on Dialysis.** Approve for 3 years.

5. **Anemia in a Patient with Chronic Kidney Disease who is not on Dialysis.** Approve for 1 year if the patient meets the following criteria (A or B):
   C) Initial Therapy. Approve if the patient meets the following criteria (i and ii):
   iii. Patient meets one of the following (a or b):
      c) Patient is ≥ 18 years of age with a hemoglobin < 10.0 g/dL; OR
      d) Patient is < 18 years of age with a hemoglobin ≤ 11.0 g/dL; AND
   iv. Patient meets one of the following (a or b):
      c) Patient is currently receiving iron therapy; OR
      d) Patient has adequate iron stores according to the prescriber; OR
   D) Patient is Currently Receiving an Erythropoiesis-Stimulating Agent. Approve if the patient meets the following criteria (i and ii):
   Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit), a darbepoetin alfa product (e.g., Aranesp), or a methoxy polyethylene glycol-epoetin beta product (e.g., Mircera).
   iii. Patient has a hemoglobin ≤ 12.0 g/dL; AND
   iv. Patient meets one of the following (a or b):
      c) Patient is currently receiving iron therapy; OR
      d) Patient has adequate iron stores according to the prescriber.

6. **Anemia in a Patient with Cancer due to Cancer Chemotherapy.** Approve for 6 months if the patient meets the following criteria (A or B):
   C) Initial Therapy. Approve if the patient meets the following criteria (i, ii, and iii):
   iv. Patient has a hemoglobin < 10.0 g/dL; AND
   v. Patient meets BOTH of the following (a and b):
      a) Patient is currently receiving myelosuppressive chemotherapy; AND
      b) According to the prescriber, myelosuppressive chemotherapy is considered non-curative; AND
   vi. Patient meets one of the following (a or b):
      c) Patient is currently receiving iron therapy; OR
      d) Patient has adequate iron stores according to the prescriber; OR
   D) Patient is Currently Receiving an Erythropoiesis-Stimulating Agent. Approve if the patient meets the following criteria (i, ii, and iii):
   Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit) or a darbepoetin alfa product (e.g., Aranesp).
   iv. Patient has a hemoglobin ≤ 12.0 g/dL; AND
   v. Patient meets BOTH of the following (a and b):
      c) Patient is currently receiving myelosuppressive chemotherapy; AND
      d) According to the prescriber, myelosuppressive chemotherapy is considered non-curative; AND
   vi. Patient meets one of the following (a or b):
      c) Patient is currently receiving iron therapy; OR
      d) Patient has adequate iron stores according to the prescriber.

4. **Anemia in a Patient with Human Immunodeficiency Virus who is Receiving Zidovudine.** Approve for 1 year if the patient meets the following criteria (A or B):
   A) Initial Therapy. Approve if the patient meets the following criteria (i, ii, and iii):
   i. Patient meets one of the following (a or b):

a) Patient has a hemoglobin < 10.0 g/dL; OR
b) Patient has a serum erythropoietin level ≤ 500 mU/mL; AND

ii. Patient is currently receiving zidovudine therapy; AND

iii. Patient meets one of the following (a or b):
a) Patient is currently receiving iron therapy; OR
b) Patient has adequate iron stores according to the prescriber; OR

B) Patient is Currently Receiving an Erythropoiesis-Stimulating Agent. Approve if the patient meets the following criteria (i, ii, and iii):
Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit) or darbepoetin alfa product (e.g., Aranesp).

iv. Patient has a hemoglobin ≤ 12.0 g/dL; AND

v. Patient is currently receiving zidovudine therapy; AND

vi. Patient meets one of the following (a or b):
a) Patient is currently receiving iron therapy; OR
b) Patient has adequate iron stores according to the prescriber.

5. Reduction of Allogeneic Red Blood Cell Transfusions in a Patient Undergoing Surgery. Approve for 1 month if the patient meets the following criteria (A, B, C, and D):
A) Hemoglobin is ≤ 13.0 g/dL; AND
B) The surgery is elective, nonvascular, and noncardiac; AND
C) Patient is not willing or able to donate autologous blood prior to surgery; AND
D) Patient meets one of the following (i or ii):
i. Patient is currently receiving iron therapy; OR
ii. Patient has adequate iron stores according to the prescriber.

Other Uses with Supportive Evidence

6. Anemia Associated with Myelodysplastic Syndrome. Approve for 1 year if the patient meets the following criteria (A or B):
C) Initial Therapy. Approve if the patient meets the following criteria (i, ii, iii, and iv):

iv. Patient is ≥ 18 years of age; AND

v. Patient meets one of the following (a or b):
a) Patient has a hemoglobin < 10.0 g/dL; OR
b) Patient has a serum erythropoietin level ≤ 500 mU/mL; AND

vi. Patient meets one of the following (a or b):
c) Patient is currently receiving iron therapy; OR
d) Patient has adequate iron stores according to the prescriber; AND

iv. The medication is prescribed by or in consultation with a hematologist or oncologist.

B) Patient is Currently Receiving an Erythropoiesis-Stimulating Agent. Approve if the patient meets the following criteria (i, ii, iii, and iv):
Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit) or a darbepoetin alfa product (e.g., Aranesp).

vii. Patient is ≥ 18 years of age; AND

viii. Patient has a hemoglobin ≤ 12.0 g/dL; AND

ix. Patient meets one of the following (a or b):
c) Patient is currently receiving iron therapy; OR
d) Patient has adequate iron stores according to the prescriber; AND

iv. The medication is prescribed by or in consultation with a hematologist or oncologist.

7. **Anemia Associated with Myelofibrosis.** Approve for the duration noted below if the patient meets the following criteria (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient meets one of the following (a or b):
       - **a)** Patient has a hemoglobin < 10.0 g/dL; OR
       - **b)** Patient has a serum erythropoietin level ≤ 500 mU/mL; AND
     - **ii.** Patient meets one of the following (a or b):
       - **a)** Patient is currently receiving iron therapy; OR
       - **b)** Patient has adequate iron stores according to the prescriber; AND
     - **iii.** The medication is prescribed by or in consultation with a hematologist or oncologist.
   - **B)** Patient is Currently Receiving an Erythropoiesis-Stimulating Agent. Approve for 1 year if the patient meets the following criteria (i, ii, iii, and iv):
     Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit) or a darbepoetin alfa product (e.g., Aranesp).
     - **i.** Patient has a hemoglobin ≤ 12.0 g/dL; AND
     - **ii.** Patient meets one of the following (a or b):
       - **a)** Patient is currently receiving iron therapy; OR
       - **b)** Patient has adequate iron stores according to the prescriber; AND
     - **iii.** According to the prescriber, patient has responded to therapy defined as hemoglobin ≥ 10 g/dL or a hemoglobin increase of ≥ 2 g/dL; AND
     - **iv.** The medication is prescribed by or in consultation with a hematologist or oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Epoetin alfa is not recommended in the following situations:

7. **Anemia Associated with Cancer in a Patient not Receiving Myelosuppressive Cancer Chemotherapy.** Epoetin alfa is not indicated in patients with cancer who are not receiving cancer chemotherapy.[1-3]

8. **Anemia Associated with Acute Myelogenous Leukemias (AML), Chronic Myelogenous Leukemias (CML) or other Myeloid Cancers.** Epoetin alfa is indicated for use in non-myeloid cancers. AML and CML are examples of myeloid cancers.[1-3]

9. **Anemia Associated with Radiotherapy in Cancer.** Epoetin alfa is not indicated for use in patients with cancer who are given only radiation therapy.[1-3]

10. **To Enhance Athletic Performance.** Epoetin alfa is not recommended for approval because this indication is excluded from coverage in a typical pharmacy benefit.

11. **Anemia due to Acute Blood Loss.** Use of Epoetin alfa is not appropriate in these types of situations.

12. **Non-Anemic Patients (Hemoglobin > 13.0 g/dL) Prior to Surgery.** Although studies have been done that involved non-anemic patients undergoing various surgeries receiving epoetin alfa preoperatively and sometimes postoperatively to prevent transfusions or subsequent anemia, the overall benefit of this therapy in those with relatively normal preoperative Hb level is questionable.

13. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

5. Procrit® intravenous or subcutaneous injection [prescribing information]. Horsham, PA: Janssen; May 2020.
6. Epogen® intravenous or subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; July 2018.
7. Retacrit® subcutaneous or intravenous injection [prescribing information]. New York, NY and Lake Forest, IL: Pfizer and Hospira; April 2023.
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PRIOR AUTHORIZATION POLICY

POLICY: Erythropoiesis-Stimulating Agents – Mircera Prior Authorization Policy
- Mircera® (methoxy polyethylene glycol-epoetin beta intravenous or subcutaneous injection – Vifor)

REVIEW DATE: 07/19/2023

OVERVIEW

Mircera, an erythropoiesis-stimulating agent (ESA), is indicated for **anemia due to chronic kidney disease** (CKD), including adults on dialysis, adults not on dialysis, and pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA.

Mircera has not been shown to improve symptoms, physical functioning, or health-related quality of life.[1] Mircera is not indicated for the following uses:
- Treatment of anemia due to cancer chemotherapy.
- As a substitute for red blood cell (RBC) transfusions in those who require immediate correction of anemia.

Therapy should be initiated for adults with CKD on dialysis when the Hb level is < 10.0 g/dL and if the Hb level approaches or exceeds 11.0 g/dL, reduce or interrupt the dose of Mircera.[1] For adults with CKD not on dialysis, consider initiating Mircera only when the Hb is < 10.0 g/dL and other considerations apply (e.g., rate of Hb decline indicates patient is likely to need RBC transfusion and reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal). If the Hb exceeds 10.0 g/dL, reduce or interrupt the Mircera dose and use the lowest dose sufficient to reduce the need for RBC transfusions.

Guidelines

The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for anemia in CKD (2012) state that for adults with CKD on dialysis ESA therapy should be used to avoid having the Hb concentration fall below 9.0 g/dL by initiating ESA therapy when the Hb is between 9.0 and 10.0 g/dL.[2] The guidelines recommend against ESA therapy for adult patients with CKD who are not on dialysis when Hb levels are ≥ 10.0 g/dL. For adult patients with CKD who are not on dialysis with Hb levels < 10.0 g/dL, the decision whether to initiate ESA therapy should be individualized based on many factors (e.g., prior response to iron therapy, the risk of needing a transfusion, presence of symptoms). In general, ESAs should not be used to maintain Hb concentrations above 11.5 g/dL in adult patients with CKD. For pediatric patients with CKD, the Hb concentration in which ESAs should be initiated in the individual patient should be considered while being aware of the potential benefits and potential harms. In all pediatric patients with CKD receiving ESA therapy, the selected Hb concentration should be in the range of 11.0 to 12.0 g/dL. Iron supplementation can improve response to ESA therapy. Baseline and periodic monitoring (e.g., iron, total iron-binding capacity, transferrin saturation, or ferritin levels) and instituting iron replacement when needed may be useful in limiting the need for ESAs, maximizing symptomatic improvement in patients, and determining the reason for inadequate response to ESAs. Iron deficiency can occur following continued ESA use. Therefore, iron supplementation is required in most patients to maintain an optimal response.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Mircera in patients with conditions other than CKD who are on dialysis. The intent of this policy is to provide recommendations for uses other than anemia in patients with CKD who are on dialysis. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mircera is recommended in those who meet one of the following criteria:

FDA-Approved Indications

7. **Anemia in a Patient with Chronic Kidney Disease who is on Dialysis.** Approve for 3 years.

8. **Anemia in a Patient with Chronic Kidney Disease who is not on Dialysis.** Approve for 1 year if the patient meets the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has a hemoglobin < 10.0 g/dL; AND
     - **iii.** Patient meets one of the following (a or b):
       - **a)** Patient is currently receiving iron therapy; OR
       - **b)** Patient has adequate iron stores according to the prescriber; OR
   - **B)** Patient is Currently Receiving an Erythropoiesis-Stimulating Agent. Approve if the patient meets the following (i, ii, and iii):
     Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit), a darbepoetin alfa product (e.g., Aranesp), or a methoxy polyethylene glycol-epoetin beta product (e.g., Mircera).
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has a hemoglobin ≤ 12.0 g/dL; AND
     - **iii.** Patient meets one of the following (a or b):
       - **a)** Patient is currently receiving iron therapy; OR
       - **b)** Patient has adequate iron stores according to the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mircera is not recommended in the following situations:

14. **Anemia Associated with Cancer in a Patient Receiving Myelosuppressive Cancer Chemotherapy.** Mircera is not indicated and not recommended for the treatment of anemia due to cancer chemotherapy.[1]

15. **To Enhance Athletic Performance.** Mircera is not recommended for approval because this indication is excluded from coverage in a typical pharmacy benefit.

16. **Anemia due to Acute Blood Loss.** Use of Mircera is not appropriate in these types of situations.

17. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

11. Mircera® intravenous or subcutaneous injection [prescribing information]. Basking Ridge, NJ: Vifor Pharma; March 2023.
12. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int.* 2012; 2(Suppl):279-335.

PRIOR AUTHORIZATION POLICY

POLICY: Fabry Disease – Galafold Prior Authorization Policy
- Galafold® (migalastat capsules – Amicus Therapeutics)

REVIEW DATE: 11/15/2023

OVERVIEW

Galafold, an oral alpha-galactosidase A (α-Gal) pharmacological chaperone, is indicated for the treatment of adults with a confirmed diagnosis of **Fabry disease** and an amenable galactosidase alpha gene (*GLA*) variant based on in vitro assay data.[1]

Disease Overview

Fabry disease is a rare inherited X-linked lysosomal storage disorder.[2-4] Absent or significantly reduced α-Gal activity leads to the accumulation of globotriaosylceramide (GL-3) in a wide variety of cells throughout the body. The accumulation of GL-3 leads to progressive multisystem disease, primarily impacting the kidney, heart, and nervous system.[3,4] Life expectancy in patients with Fabry disease is reduced; median survival is typically 50 to 55 years in men and 70 years in women.[2]

Currently, there have been more than 800 mutations to the gene encoding α-Gal identified.[5] About 60% are missense mutations resulting in single amino acid substitutions. Some of these mutated enzymes have activity levels similar to normal α-Gal; however, they have been found to be unstable and are retained in the endoplasmic reticulum.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Galafold. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Galafold as well as the monitoring required for adverse events and long-term efficacy, approval requires Galafold to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Galafold is recommended in those who meet the following criteria:

FDA-Approved Indication

33. Fabry Disease. Approve for 1 year if the patient meets the following (A, B, and C):
- ~~**16.**~~ Patient is ≥ 18 years of age; AND
- ~~**17.**~~ Patient has an amenable galactosidase alpha gene (*GLA*) variant based on in vitro assay data; AND
- **18.** The medication is prescribed by or in consultation with a geneticist, nephrologist, or a physician who specializes in the treatment of Fabry disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Galafold is not recommended in the following situations:

10. **Concurrent Use with Fabrazyme (agalsidase beta intravenous infusion).** One small study (n = 23) assessed a single dose of Galafold (150 mg or 450 mg) used concurrently with Fabrazyme or agalsidase alpha. While a single dose of Galafold significantly increased α-Gal activity, the long-term safety and efficacy of concurrent use of Galafold and Fabrazyme has not been established.[6] Galafold is not FDA approved for concurrent use with Fabrazyme.

11. **Concurrent Use with Elfabrio (pegunigalsidase alfa intravenous infusion).** Galafold has not been evaluated for use in combination with Elfabrio. It is not FDA approved for concurrent use with enzyme replacement therapy.

12. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

101. Galafold® capsules [prescribing information]. Cranbury, NJ: Amicus Therapeutics; June 2023.
102. Schiffmann R. Fabry Disease. *Handb Clin Neurol*. 2015;132:231-248.
103. Arends M, Wanner C, Hughes D, et al. Characterization of Classical and Nonclassical Fabry Disease: A Multinational Study. *J Am Soc Nephrol*. 2017;28:1631-1641.
104. Laney DA, Bennett RL, Clarke V, et al. Fabry Disease Practice Guidelines: Recommendations of the National Society of Genetic Counselors. *J Genet Counsel*. 2013;22:555-564.
105. Benjamin ER, Della Valle MC, Wu X, et al. The Validation of Pharmacogenetics for the Identification of Fabry Patients to be Treated with Migalastat. *Genet Med*. 2017;19:430-438.
106. Warnock DG, Bichet DG, Holida M, et al. Oral Migalastat HCl Leads to Greater Systemic Exposure and Tissue Levels of Active α-Galactosidase A in Fabry Patients when Co-Administered with Infused Agalsidase. *PLoS ONE*. 2015;10: e0134341.

PRIOR AUTHORIZATION POLICY

POLICY: Gamifant Prior Authorization Policy
- Gamifant® (emapalumab-lzsg intravenous infusion – Sobi)

REVIEW DATE: 01/03/2024

OVERVIEW

Gamifant, an anti-interferon gamma (IFN-γ) antibody, is indicated for the treatment of **primary hemophagocytic lymphohistiocytosis** (HLH) in adult and pediatric patients with refractory, recurrent, or progressive disease or intolerance with conventional HLH therapy.[1]

Disease Overview

HLH is a syndrome characterized by signs and symptoms of extreme inflammation, caused by defects in cytotoxic function (cytotoxic T cells and natural killer cells).[2] The incidence is estimated at 1.2 cases per million individuals per year, but this is likely an underestimate.[3] In healthy individuals, cytotoxic function is important to terminate immune responses when appropriate by targeting and destroying activated immune cells. Deficiencies in cytotoxic function lead to an unchecked immune response and hyper-inflammation. Primary HLH has a clear genetic cause, whereas secondary HLH is triggered by a concomitant infection or medical condition, such as Epstein-Barr virus infection, malignancy, or rheumatologic disorders. IFN-γ normally has both pro-inflammatory functions (e.g., macrophage activation) and anti-inflammatory functions (e.g., activation of cytotoxic cells).[4,5] However, in HLH, the anti-inflammatory action of IFN-γ is ineffective due to impaired cytotoxic cell activity; thus, pro-inflammatory effects predominate.

Guidelines

The HLH-2004 treatment protocol, developed by the Histiocyte Society, is the current standard of care for diagnostic and therapeutic guidelines.[6] Gamifant is not addressed in the 2004 protocol. To establish a diagnosis of HLH, patients must either have a molecular diagnosis consistent with HLH or meet five out of eight diagnostic criteria. A backbone of etoposide and systemic dexamethasone is the conventional standard of care to induce symptomatic resolution; cyclosporine A and anti-thymocyte globulin have also demonstrated efficacy. Although chemotherapy prolongs survival in primary HLH, a hematopoietic stem cell transplant (HSCT) is needed for cure. Patients with primary HLH should continue chemotherapy (usually with etoposide, cyclosporine A, and dexamethasone) until HSCT can be performed. Myelotoxicity due to chemotherapy is a concern, especially since patients with HLH can have severe cytopenias and immunodeficiency at baseline.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Gamifant. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Gamifant, approval requires it to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Gamifant is recommended for those who meet the following criteria:

FDA-Approved Indication

4. Hemophagocytic Lymphohistiocytosis, Primary. Approve Gamifant for 6 months if the patient meets all of the following (A, B, C, and D):

A) Patient has a diagnosis of hemophagocytic lymphohistiocytosis determined by at least one of the following (i or ii):

i. Patient has a molecular genetic diagnosis consistent with hemophagocytic lymphohistiocytosis; OR

ii. Prior to treatment, the patient meets at least FIVE of the following diagnostic criteria at baseline (FIVE of a, b, c, d, e, f, g, or h):

a) Fever ≥ 38.5° C; OR

b) Splenomegaly; OR

c) Cytopenias defined as at least TWO of the following (TWO of 1, 2, or 3):

1) Hemoglobin < 9 g/dL (or < 10 g/dL in infants less than 4 weeks of age);

2) Platelets < 100 x 10^9/L; OR

3) Neutrophils < 1.0 x 10^9/L; OR

d) Patient meets one of the following (1 or 2):

1) Fasting triglycerides ≥ 265 mg/dL; OR

2) Fibrinogen ≤ 1.5 g/L; OR

e) Hemophagocytosis in bone marrow, spleen, or lymph nodes; OR

f) Low or absent natural killer cell activity (according to local laboratory reference); OR

g) Ferritin ≥ 500 mcg/L; OR

h) Soluble CD25 (i.e., soluble interleukin-2 receptor) ≥ 2,400 U/mL; AND

B) Patient has tried at least one conventional therapy (e.g., etoposide, cyclosporine A, or anti-thymocyte globulin); AND

C) According to the prescriber, the patient has experienced at least ONE of the following (i or ii):

i. Refractory, recurrent, or progressive disease during conventional therapy (e.g., etoposide, cyclosporine A, or anti-thymocyte globulin); OR

ii. Intolerance to conventional therapy (e.g., etoposide, cyclosporine A, or anti-thymocyte globulin); AND

D) The medication is prescribed by or in consultation with a hematologist, oncologist, immunologist, transplant specialist, or physician who specializes in hemophagocytic lymphohistiocytosis or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Gamifant is not recommended in the following situations:

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Gastroenterology – Gattex Prior Authorization Policy
- Gattex® (teduglutide subcutaneous injection – Shire)

REVIEW DATE: 06/28/2023

OVERVIEW

Gattex, a glucagon-like peptide-2 (GLP-2) analog, is indicated for the treatment of **short bowel syndrome** in patients ≥ 1 year of age who are dependent on parenteral support.[1]

Clinical Efficacy

In a study involving adults (n = 86) with short bowel syndrome requiring parenteral support at least 3 days per week, more patients treated with Gattex through Month 6 achieved ≥ 20% reduction in weekly intravenous volume (63% vs. 30% with placebo).[1] The mean reduction in intravenous volume was 4.4 liters with Gattex vs. 2.3 liters with placebo. When treated over an additional 2 years, the mean reduction from baseline was 7.55 liters. Ten patients were weaned off of nutritional support and remained on Gattex therapy. At Week 24 of a pediatric study, 69% of patients (n = 18/26) reduced parenteral support volume by at least 20% with Gattex. The mean reduction in intravenous volume was -23 mL/kg/day, a 42% reduction in parenteral support. Three patients were weaned off of parenteral nutritional support.

Safety

Gattex has Warnings and Precautions regarding acceleration of neoplastic growth, colorectal polyps, intestinal obstruction, biliary and pancreatic disease, fluid overload (including congestive heart failure), and potential for increased absorption of concomitant oral medications, particularly those with a narrow therapeutic index.[1] It was approved with a Risk Evaluation and Mitigation Strategy (REMS) program intended to inform healthcare providers and patients about serious risks, including the risks of possible acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction, and biliary and pancreatic disorders.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Gattex. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Gattex as well as the monitoring required for adverse events and long-term efficacy, approval requires Gattex to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Gattex is recommended in those who meet the following criteria:

FDA-Approved Indication

31. Short Bowel Syndrome. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

- **i.** Patient is ≥ 1 year of age; AND
- **ii.** Patient meets ONE of the following (a or b):
  - **a)** Patient is currently receiving parenteral nutrition on 3 or more days per week; OR
  - **b)** According to the prescriber, the patient is unable to receive adequate total parenteral nutrition (TPN) required for caloric needs; AND
- **iii.** The medication is prescribed by or in consultation with a gastroenterologist.

B) Patient is Currently Receiving Gattex. Approve for 1 year if the patient meets all of the following (i, ii, and iii):

- **i.** Patient has already received at least 6 months of therapy with Gattex; AND
  Note: A patients who has received < 6 months of continuous therapy should be considered under criterion 1A (Initial Therapy).
- **ii.** According to the prescriber, the patient has experienced at least a 20% decrease from baseline in the weekly volume of parenteral nutrition; AND
- **iii.** The medication is prescribed by or in consultation with a gastroenterologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Gattex is not recommended in the following situations:

70. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

309. Gattex® subcutaneous injection [prescribing information]. Lexington, MA: Shire; October 2022.
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PRIOR AUTHORIZATION POLICY

POLICY: Gaucher Disease – Enzyme Replacement Therapy – Cerezyme Prior Authorization Policy
- Cerezyme® (imiglucerase intravenous infusion – Genzyme)

REVIEW DATE: 04/05/2023

OVERVIEW

Cerezyme, an analogue of β-glucocerebrosidase, is indicated for the long-term enzyme replacement therapy for patients with a confirmed diagnosis of **Type 1 Gaucher disease** that results in at least one of the following: anemia, thrombocytopenia, bone disease, hepatomegaly, or splenomegaly.[1]

Cerezyme is produced via recombinant DNA technology in Chinese hamster ovary cells and differs from human placental glucocerebrosidase by one amino acid at position 495.[1] Cerezyme catalyzes the breakdown of glucocerebroside to glucose and ceramide.

Disease Overview

Gaucher disease is a rare autosomal recessive, inherited, lysosomal storage disorder caused by a deficiency of the lysosomal enzyme β-glucocerebrosidase.[2-4] Glucocerebrosidase is responsible for the breakdown of glucosylcerebroside (GluCer) into glucose and ceramide. A deficiency of this enzyme is characterized by an excessive accumulation of GluCer in the visceral organs such as the liver, spleen, and bone marrow. GluCer remains stored within lysosomes causing enlarged lipid-laden macrophages called "Gaucher cells".

Gaucher disease is classified into three phenotypes (Types 1 through 3).[2-5] Type 1 is a non-neuropathic variant with asymptomatic or symptomatic clinical manifestations of splenomegaly, hepatomegaly, anemia, thrombocytopenia, skeletal complications, and occasional lung involvement. Type 2 is an acute neuropathic form characterized by an early onset (3 to 6 months of age) of rapidly progressive neurological disease with visceral manifestations; death generally occurs by the time patients reach 1 to 2 years of age. Type 3 is characterized by neurological symptoms and visceral symptoms with a later onset and includes abnormal eye movements, ataxia, seizures, and dementia. Type 1 is most prevalent in the Western world, accounting for an estimated 94% of patients with Gaucher disease.[2,6] Types 2 and 3 represent < 1% and 5%, respectively, in Europe, North America, and Israel.[2,5] The diagnosis of Gaucher disease is established by demonstrating deficient β-glucocerebrosidase activity in leukocytes or fibroblasts, or mutations in the glucocerebrosidase gene.[7,8]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cerezyme. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cerezyme as well as the monitoring required for adverse events and long-term efficacy, approval requires Cerezyme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cerezyme is recommended in those who meet the following criteria:

FDA-Approved Indication

32. Gaucher Disease. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient has Type 1 Gaucher disease; AND
- **B)** The diagnosis is established by one of the following (i or ii):
  - **i.** Demonstration of deficient β-glucocerebrosidase activity in leukocytes or fibroblasts; OR
  - **ii.** Molecular genetic testing documenting glucocerebrosidase gene mutation; AND
- **C)** Cerezyme is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cerezyme is not recommended in the following situations:

71. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

311. Cerezyme® intravenous infusion [prescribing information]. Cambridge, MA: Genzyme; January 2022.
312. Burrow TA, Barnes S, and Grabowski GA. Prevalence and management of Gaucher disease. *Pediatric Health Med Ther*. 2011;2:59-73.
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314. Jmoudiak, M. and Futerman, AH. Gaucher disease: Pathological mechanisms and modern management. *Br J Haematol*. 2005;129(2):178–188.
315. Grabowski GA. Lysosomal storage disease 1- phenotype, diagnosis, and treatment of Gaucher's disease. *Lancet*. 2008;372:1263-1271.
316. Zimran A. How I treat Gaucher disease. *Blood*. 2011;118:1463-1471.
317. Stirnemann J, Belmatoug N, Camou F, et al. A review of Gaucher disease pathophysiology, clinical presentation and treatments. *Int J Mol Sci*. 2017;18:441.
318. Baris HN, Cohen IJ, Mistry PK. Gaucher disease: The metabolic defect, pathophysiology, phenotypes and natural . *Pediatr Endocrinol Rev*. 2014;12:72-81.

PRIOR AUTHORIZATION POLICY

POLICY: Gaucher Disease – Enzyme Replacement Therapy – Elelyso Prior Authorization Policy
- Elelyso® (taliglucerase intravenous infusion – Pfizer)

REVIEW DATE: 04/05/2023

OVERVIEW

Elelyso, an analogue of β-glucocerebrosidase, is indicated for the treatment of patients ≥ 4 years of age with a confirmed diagnosis of **Type 1 Gaucher disease**.[1]

Elelyso is produced via recombinant DNA technology in genetically modified carrot plant root cells.[1] Elelyso differs from human glucocerebrosidase by two amino acids at the N terminal and seven amino acids at the C terminal end of the protein. Elelyso catalyzes the breakdown of glucocerebroside to glucose and ceramide.

Disease Overview

Gaucher disease is a rare autosomal recessive, inherited, lysosomal storage disorder caused by a deficiency of the lysosomal enzyme β-glucocerebrosidase.[2-4] Glucocerebrosidase is responsible for the breakdown of glucosylcerebroside (GluCer) into glucose and ceramide. A deficiency of this enzyme is characterized by an excessive accumulation of GluCer in the visceral organs such as the liver, spleen, and bone marrow. GluCer remains stored within lysosomes causing enlarged lipid-laden macrophages called "Gaucher cells".

Gaucher disease is classified into three phenotypes (Types 1 through 3).[2-5] Type 1 is a non-neuropathic variant with asymptomatic or symptomatic clinical manifestations of splenomegaly, hepatomegaly, anemia, thrombocytopenia, skeletal complications, and occasional lung involvement. Type 2 is an acute neuropathic form characterized by an early onset (3 to 6 months of age) of rapidly progressive neurological disease with visceral manifestations; death generally occurs by the time patients reach 1 to 2 years of age. Type 3 is characterized by neurological symptoms and visceral symptoms with a later onset and includes abnormal eye movements, ataxia, seizures, and dementia. Type 1 is most prevalent in the Western world, accounting for an estimated 94% of patients with Gaucher disease.[2,6] Types 2 and 3 represent < 1% and 5%, respectively, in Europe, North America, and Israel.[2,5] The diagnosis of Gaucher disease is established by demonstrating deficient β-glucocerebrosidase activity in leukocytes or fibroblasts, or mutations in the glucocerebrosidase gene.[7,8]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Elelyso. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Elelyso as well as the monitoring required for adverse events and long-term efficacy, approval requires Elelyso to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Elelyso is recommended in those who meet the following criteria:

FDA-Approved Indication

33. Gaucher Disease. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient has Type 1 Gaucher disease; AND
- **B)** Patients is ≥ 4 years of age; AND
- **C)** The diagnosis is established by one of the following (i or ii):
  - **i.** Demonstration of deficient β-glucocerebrosidase activity in leukocytes or fibroblasts; OR
  - **ii.** Molecular genetic testing documenting glucocerebrosidase gene mutation; AND
- **D)** Elelyso is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage for Elelyso is not recommended in the following situations:

72. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

319. Elelyso® intravenous infusion [prescribing information]. New York, NY: Pfizer; July 2021.
320. Burrow TA, Barnes S, and Grabowski GA. Prevalence and management of Gaucher disease. *Pediatric Health Med Ther*. 2011;2:59-73.
321. Cox T. Gaucher disease: clinical profile and therapeutic development. *Biologics*. 2010;4:299-313.
322. Jmoudiak, M. and Futerman, AH. Gaucher disease: Pathological mechanisms and modern management. *Br J Haematol*. 2005;129(2):178–188.
323. Grabowski GA. Lysosomal storage disease 1- phenotype, diagnosis, and treatment of Gaucher's disease. *Lancet*. 2008;372:1263-1271.
324. Zimran A. How I treat Gaucher disease. *Blood*. 2011;118:1463-1471.
325. Stirnemann J, Belmatoug N, Camou F, et al. A review of Gaucher disease pathophysiology, clinical presentation and treatments. *Int J Mol Sci*. 2017;18:441.
326. Baris HN, Cohen IJ, Mistry PK. Gaucher disease: The metabolic defect, pathophysiology, phenotypes and natural . *Pediatr Endocrinol Rev*. 2014;12:72-81.

PRIOR AUTHORIZATION POLICY

POLICY: Gaucher Disease – Enzyme Replacement Therapy – Vpriv Prior Authorization Policy
- Vpriv® (velaglucerase intravenous infusion – Shire Human Genetic Therapies)

REVIEW DATE: 04/05/2023

OVERVIEW

Vpriv, an analogue of β-glucocerebrosidase, is indicated for long-term enzyme replacement therapy for patients with **Type 1 Gaucher disease**.[1]

Vpriv is produced via gene activation technology in a human fibroblast cell line.[1] Vpriv has the same amino acid sequence as the naturally occurring human glucocerebrosidase. Vpriv catalyzes the breakdown of glucocerebroside to glucose and ceramide.

Disease Overview

Gaucher disease is a rare autosomal recessive, inherited, lysosomal storage disorder caused by a deficiency of the lysosomal enzyme β-glucocerebrosidase.[2-4] Glucocerebrosidase is responsible for the breakdown of glucosylcerebroside (GluCer) into glucose and ceramide. A deficiency of this enzyme is characterized by an excessive accumulation of GluCer in the visceral organs such as the liver, spleen, and bone marrow. GluCer remains stored within lysosomes causing enlarged lipid-laden macrophages called "Gaucher cells".

Gaucher disease is classified into three phenotypes (Types 1 through 3).[2-5] Type 1 is a non-neuropathic variant with asymptomatic or symptomatic clinical manifestations of splenomegaly, hepatomegaly, anemia, thrombocytopenia, skeletal complications, and occasional lung involvement. Type 2 is an acute neuropathic form characterized by an early onset (3 to 6 months of age) of rapidly progressive neurological disease with visceral manifestations; death generally occurs by the time patients reach 1 to 2 years of age. Type 3 is characterized by neurological symptoms and visceral symptoms with a later onset and includes abnormal eye movements, ataxia, seizures, and dementia. Type 1 is most prevalent in the Western world, accounting for an estimated 94% of patients with Gaucher disease.[2,6] Types 2 and 3 represent < 1% and 5%, respectively, in Europe, North America, and Israel.[2,5] The diagnosis of Gaucher disease is established by demonstrating deficient β-glucocerebrosidase activity in leukocytes or fibroblasts, or mutations in the glucocerebrosidase gene.[7,8]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vpriv. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vpriv as well as the monitoring required for adverse events and long-term efficacy, approval requires Vpriv to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vpriv is recommended in those who meet the following criteria:

FDA-Approved Indication

34. Gaucher Disease. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient has Type 1 Gaucher disease; AND
- **B)** The diagnosis is established by one of the following (i or ii):
  - **i.** Demonstration of deficient β-glucocerebrosidase activity in leukocytes or fibroblasts; OR
  - **ii.** Molecular genetic testing documenting glucocerebrosidase gene mutation; AND
- **C)** Vpriv is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vpriv is not recommended in the following situations:

73. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

327. Vpriv® intravenous infusion [prescribing information]. Lexington, MA: Shire Human Genetic Therapies; December 2020.
328. Burrow TA, Barnes S, and Grabowski GA. Prevalence and management of Gaucher disease. *Pediatric Health Med Ther*. 2011;2:59-73.
329. Cox T. Gaucher disease: clinical profile and therapeutic development. *Biologics*. 2010;4:299-313.
330. Jmoudiak, M. and Futerman, AH. Gaucher disease: Pathological mechanisms and modern management. *Br J Haematol*. 2005;129(2):178–188.
331. Grabowski GA. Lysosomal storage disease 1- phenotype, diagnosis, and treatment of Gaucher's disease. *Lancet*. 2008;372:1263-1271.
332. Zimran A. How I treat Gaucher disease. *Blood*. 2011;118:1463-1471.
333. Stirnemann J, Belmatoug N, Camou F, et al. A review of Gaucher disease pathophysiology, clinical presentation and treatments. *Int J Mol Sci*. 2017;18:441.
334. Baris HN, Cohen IJ, Mistry PK. Gaucher disease: The metabolic defect, pathophysiology, phenotypes and natural . *Pediatr Endocrinol Rev*. 2014;12:72-81.

PRIOR AUTHORIZATION POLICY

POLICY: Gaucher Disease – Substrate Reduction Therapy – Cerdelga Prior Authorization Policy
- Cerdelga® (eliglustat capsules – Genzyme)

REVIEW DATE: 05/10/2023

OVERVIEW

Cerdelga, a glucosylceramide synthase inhibitor, is indicated for the long-term treatment of adults with **Gaucher disease type 1** who are cytochrome P450 2D6 extensive metabolizers, intermediate metabolizers, or poor metabolizers as detected by an FDA-cleared test.[1]

Disease Overview

Gaucher disease is caused by a deficiency in the lysosomal enzyme β-glucocerebrosidase.[1] This enzyme is responsible for the breakdown of glucosylceramide into glucose and ceramide. In Gaucher disease, deficiency of the enzyme β-glucocerebrosidase results in the accumulation of glucosylceramide substrate in the lysosomal compartment of macrophages, giving rise to foam cells or "Gaucher cells." Cerdelga is a specific inhibitor of the enzyme glycosylceramide synthase, which is responsible for producing the substrate glucosylceramide; hence Cerdelga functions as a substrate reduction therapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cerdelga. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cerdelga as well as the monitoring required for adverse events and long-term efficacy, approval requires Cerdelga to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cerdelga is recommended in those who meet the following criteria:

FDA-Approved Indication

34. Gaucher Disease Type 1. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is a cytochrome P450 2D6 extensive metabolizer, intermediate metabolizer, or poor metabolizer as detected by an approved test; AND
- **B)** The diagnosis is established by one of the following (i or ii):
  - **i.** Demonstration of deficient beta-glucocerebrosidase activity in leukocytes or fibroblasts; OR
  - **ii.** Molecular genetic testing documenting glucocerebrosidase gene mutation; AND
- **C)** The medication is prescribed by or in consultation with a geneticist, endocrinologist, metabolic disorder subspecialist, or a physician who specializes in the treatment of Gaucher disease or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cerdelga is not recommended in the following situations:

13. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

50. Cerdelga® capsules [prescribing information]. Waterford, Ireland: Genzyme; July 2021.

PRIOR AUTHORIZATION POLICY

POLICY: Gaucher Disease – Substrate Reduction Therapy – Miglustat Prior Authorization Policy
- Zavesca® (miglustat capsules – Actelion, generic)

REVIEW DATE: 05/10/2023

OVERVIEW

Miglustat capsules (Zavesca, generic), a glucosylceramide synthase inhibitor, is indicated as monotherapy for the treatment of adults with mild to moderate **Gaucher disease type 1** for whom enzyme replacement therapy is not a therapeutic option (e.g., due to allergy, hypersensitivity, or poor venous access).[1]

Disease Overview

Gaucher disease is caused by a deficiency in the lysosomal enzyme β-glucocerebrosidase.[2] This enzyme is responsible for the breakdown of glucosylceramide into glucose and ceramide. In Gaucher disease, deficiency of the enzyme β-glucocerebrosidase results in the accumulation of glucosylceramide substrate in lysosomal compartment of macrophages, giving rise to foam cells or "Gaucher cells." Zavesca is a specific inhibitor of the enzyme glycosylceramide synthase, which is responsible for producing the substrate glucosylceramide.[1] By functioning as a substrate reduction therapy, Zavesca allows the residual activity of the deficient glucocerebrosidase enzyme to be more effective.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of miglustat capsules (Zavesca, generic). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with miglustat capsules as well as the monitoring required for adverse events and long-term efficacy, approval requires miglustat capsules to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of miglustat capsules (Zavesca, generic) is recommended in those who meet the following criteria:

FDA-Approved Indication

35. Gaucher Disease Type 1. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** The diagnosis is established by one of the following (i or ii):
  - **i.** Demonstration of deficient beta-glucocerebrosidase activity in leukocytes or fibroblasts; OR
  - **ii.** Molecular genetic testing documenting glucocerebrosidase gene mutation; AND
- **B)** The medication is prescribed by or in consultation with a geneticist, endocrinologist, metabolic disorder subspecialist, or a physician who specializes in the treatment of Gaucher disease or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of miglustat capsules (Zavesca, generic) is not recommended in the following situations:

14. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

51. Zavesca® capsules [prescribing information]. South San Francisco, CA: Actelion; August 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Gonadotropin-Releasing Hormone Agonist – Synarel Prior Authorization Policy
- Synarel® (nafarelin acetate nasal solution – Pfizer)

REVIEW DATE: 12/20/2023

OVERVIEW

Synarel, a gonadotropin-releasing hormone (GnRH) agonist, is indicated for the following:[1]

- **Central precocious puberty**, treatment in children of both sexes.
- **Endometriosis management**, including pain relief and reduction of endometriotic lesions. Experience with Synarel for this indication is limited to women ≥ 18 years of age treated for 6 months.

Guidelines

GnRH agonists are the standard of care for the treatment of central precocious puberty.[2-4] The European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society convened a consensus conference to review the use of GnRH agonists in pediatric patients with central precocious puberty (2009).[2] The panel noted that the available GnRH agonists (including nafarelin) are effective despite different routes of administration, dosing, and duration of action. In addition, the various GnRH agonists are well-tolerated in children and adolescents. An update by an International Consortium (2019) notes the lack of prospective comparative studies to establish differences in efficacy (if any) among the various GnRH agonists.[3] Discontinuation of GnRH agonist therapy should be individualized, based on the patient's readiness for resumption of puberty, recent growth rates, and shifts in height prediction.

The American College of Obstetricians and Gynecologists (ACOG) practice bulletin on the management of endometriosis (2010, reaffirmed 2018) notes that empiric treatment with a GnRH agonist is appropriate after an appropriate pretreatment evaluation (to exclude other causes of chronic pelvic pain) and failure of initial treatment with oral contraceptives and non-steroidal anti-inflammatory drugs.[5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Synarel. All approvals are provided for 1 year in duration unless otherwise noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Synarel is recommended in those who meet one of the following criteria:

FDA-Approved Indications

17. Central Precocious Puberty. Approve for 1 year.

18. Endometriosis. Approve for 6 months if the patient meets the following (A and B):

a) Patient is ≥ 18 years of age; AND

b) Patient has tried one of the following, unless contraindicated (i, ii, or iii):

i. A contraceptive; OR
   Note: Examples of contraceptives include combination oral contraceptives, levonorgestrel-releasing intrauterine systems [e.g., Mirena®, Liletta®]).

ii. An oral progesterone (e.g., norethindrone tablets); OR

iii. A depo-medroxyprogesterone injection.
   Note: An exception to the requirement for a trial of the above therapies can be made if the patient has previously used a gonadotropin-releasing hormone (GnRH) agonist (e.g., Lupron Depot) or antagonist (e.g., Orilissa) for endometriosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Synarel is not recommended in the following situations:

3. Peripheral Precocious Puberty (Also Known as Gonadotropin-Releasing Hormone-Independent Precocious Puberty). Children with peripheral precocious puberty do not respond to GnRH agonist therapy.[2] Treatment is directed at removing or blocking the production and/or response to the excess sex steroids, depending on the cause (e.g., surgically removing human chorionic gonadotropin-secreting tumors or using glucocorticoids to treat defects in adrenal steroidogenesis [such as classic congenital adrenal hyperplasia]).

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1 Synarel® nasal spray [prescribing information]. New York, NY: Pfizer; January 2023.

2 Carel JC, Eugster EA, Rogol A, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics.* 2009;123(4):e752-762.

3 Krishna KB, Fuqua JS, Rogol AD, et al. Use of gonadotropin-releasing hormone analogs in children: update by an international consortium. *Horm Res Paediatr*. 2019;91:357-372.

4 Eugster EA. Treatment of central precocious puberty. *J Endo Soc*. 2019;3:965-972.

5 Management of Endometriosis. ACOG Practice Bulletin. Clinical Management Guidelines for Obstetrician-Gynecologists. Number 114, July 2010. (Reaffirmed 2018) *Obstetrics & Gynecology*. 2010;116(1):223-236.

PRIOR AUTHORIZATION POLICY

POLICY: Gonadotropin-Releasing Hormone Agonists – Central Precocious Puberty Prior Authorization Policy

- Fensolvi® (leuprolide acetate subcutaneous injection, extended-release – Tolmar)
- Lupron Depot-Ped® (leuprolide acetate depot intramuscular injection – AbbVie)
- Triptodur™ (triptorelin intramuscular injection, extended-release – Azurity)

REVIEW DATE: 11/08/2023

OVERVIEW

Fensolvi, Lupron Depot-Ped, and Triptodur are gonadotropin-releasing hormone (GnRH) agonists indicated for the **treatment of pediatric patients with central precocious puberty**.[1-3] Fensolvi is administered by a subcutaneous injection and both Lupron Depot-Ped and Triptodur are administered by intramuscular injection. Fensolvi is administered once every 6 months, Lupron Depot-Ped is administered once a month, once every 3 months (or 12 weeks), or once every 6 months (24 weeks), and Triptodur is administered once every 24 weeks.

GnRH agonists can also be used off-label for the **treatment of gender-dysphoric/gender-incongruent persons** to suppress physical changes of puberty and gonadal function.[7,8] Pubertal hormonal suppression should typically be initiated after the adolescent first exhibits physical changes of puberty (Tanner stages G2/B2). Long-acting GnRH analogs are the currently preferred treatment option. An advantage to using a GnRH analog is that the effects can be reversed; pubertal suppression can be discontinued if the individual no longer wishes to transition. Upon discontinuation of therapy, spontaneous pubertal development has been shown to resume. GnRH analogs can also be used in patients during late puberty to suppress the hypothalamic-pituitary-gonadal axis to allow for lower doses of cross-sex hormones.[9] In addition to use in adolescents, GnRH analog therapy is also used in adults, particularly male-to-female patients.[10]

Guidelines

The standard of care for central precocious puberty is GnRH agonists.[4-6] The European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society convened a consensus conference to review the use of GnRH agonists in pediatric patients with central precocious puberty (2009).[4] The panel noted that the available GnRH agonists (including leuprolide and triptorelin) are effective despite different routes of administration, dosing, and duration of action. In addition, the various GnRH agonists are well-tolerated in children and adolescents. An update by an International Consortium (2019) notes the lack of prospective comparative studies to establish differences in efficacy (if any) among the various GnRH agonists.[5] The Consortium does not prefer one GnRH agonist over another. Discontinuation of GnRH agonist therapy should be individualized, based on the patient's readiness for resumption of puberty, recent growth rates, and shifts in height prediction.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of gonadotropin-releasing hormone agonists (Fensolvi, Lupron Depot-Ped, and Triptodur). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of gender-dysphoric/gender-incongruent persons treated with Fensolvi, Lupron Depot-Ped, or Triptodur as well as the monitoring required for adverse events and long-term efficacy, approval requires that the product be prescribed by or in consultation with a physician who specializes in this condition.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of a gonadotropin-releasing hormone agonist (Fensolvi, Lupron Depot-Ped, and Triptodur) is recommended in those who meet one of the following criteria:

FDA-Approved Indication

21. **Central Precocious Puberty.** Approve the requested gonadotropin-releasing hormone agonist for 1 year.

Other Uses with Supportive Evidence

22. **Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Gender Reassignment (Female-To-Male or Male-To-Female).** Approve the requested gonadotropin-releasing hormone agonist for 1 year if prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of transgender patients.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of a gonadotropin-releasing hormone agonist (Fensolvi, Lupron Depot-Ped, and Triptodur) is not recommended in the following situations:

15. **Peripheral Precocious Puberty (Also Known as GnRH-Independent Puberty)**. Children with peripheral precocious puberty do not respond to GnRH agonist therapy.[4] Treatment is directed at removing or blocking the production and/or response to the excess sex steroids, depending on the cause (e.g., surgically removing human chorionic gonadotropin-secreting tumors or using glucocorticoids to treat defects in adrenal steroidogenesis [such as classic congenital adrenal hyperplasia]).

16. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

231. Lupron Depot-Ped® [prescribing information]. North Chicago, IL; AbbVie; April 2023.
232. Triptodur™ [prescribing information]. Woburn, MA: Azurity; December 2022.
233. Fensolvi® [prescribing information]. Fort Collins, CO: Tolmar; April 2023.
234. Carel JC, Eugster EA, Rogol A, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics.* 2009;123(4):e752-762.
235. Krishna KB, Fuqua JS, Rogol AD, et al. Use of gonadotropin-releasing hormone analogs in children: update by an international consortium. *Horm Res Paediatr*. 2019;91:357-372.
236. Eugster EA. Treatment of central precocious puberty. *J Endo Soc*. 2019;3:965-972.
237. Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guidelines. *J Clin Endocrinol Metab*. 2017;102:3869-3903.
238. World Professional Association for Transgender Health (WPATH). Standards of Care for the health of transgender and gender diverse people (version 8). Available at: https://www.wpath.org/publications/soc. Accessed on November 6, 2023.
239. Rosenthal SM. Approach to the patient: transgender youth: endocrine considerations. *J Clin Endocrine Metab*. 2014;99:4379-4389.
240. Spack NP. Management of transgenderism. *JAMA*. 2013;309:478-484.

PRIOR AUTHORIZATION POLICY

POLICY: Gonadotropin-Releasing Hormone Agonists – Implants Prior Authorization Policy
- Supprelin® LA (histrelin acetate subcutaneous implant – Endo)
- Vantas® (histrelin acetate subcutaneous implant – Endo [discontinued])
- Zoladex® (goserelin acetate subcutaneous implant – TerSera Therapeutics)

REVIEW DATE: 02/15/2023

OVERVIEW

Supprelin LA, Vantas, and Zoladex are gonadotropin-releasing hormone (GnRH) agonist implants.[1-4]

Supprelin LA is indicated for the treatment of children with **central precocious puberty**.[1]

Vantas is indicated for the palliative treatment of **advanced prostate cancer**.[2] Although Vantas is not indicated for use in children with central precocious puberty, it contains the same chemical entity as Supprelin LA and can be used for this condition. Endo discontinued the manufacturing of Vantas as of 9/21/2021.[10]

Zoladex is indicated for the following conditions.[3,4] Zoladex 3.6 mg (equivalent to 3.8 mg goserelin acetate) is approved for all the diagnoses below. Zoladex 10.8 mg (equivalent to 11.3 mg goserelin acetate) is only indicated for prostate cancer.

- **Breast cancer**, palliative treatment of advanced breast cancer in pre- and perimenopausal women (Zoladex 3.6 mg implant only).
- **Endometrial-thinning**, use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding (Zoladex 3.6 mg implant only).
- **Endometriosis**, including pain relief and reduction of endometriotic lesions for the duration of therapy (Zoladex 3.6 mg implant only).
- **Prostate cancer**, in combination with flutamide for the management of locally confined Stage T2b-T4 (Stage B2-C).
- **Prostate cancer**, advanced carcinoma or palliative treatment.

Guidelines

The GnRH agonists are addressed in treatment guidelines:

- **Breast cancer:** The National Comprehensive Cancer Network (NCCN) breast cancer guidelines (version 1.2023 – January 27, 2023) do not note the use of Zoladex implants for advanced breast cancer.[5] However, the guidelines note that GnRH agonists (e.g., goserelin) administered prior to initiating chemotherapy protect against ovarian failure and reduce the risk of early menopause. Ovarian suppression may be recommended in patients who are premenopausal at diagnosis.
- **Central precocious puberty**, also known as gonadotropin-dependent precocious puberty, is caused by early maturation of the hypothalamic-pituitary-gonadal axis.[6] The standard of care for central precocious puberty is GnRH agonists. The European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society convened a consensus conference (2009) to review the use of GnRH agonists in pediatric patients with central precocious puberty.[7] The panel noted that the available GnRH agonists (including leuprolide, triptorelin, and histrelin implant) are effective despite different routes of administration, dosing, and duration of action. An update by the International Consortium (2019) reiterates the use of GnRH agonists (e.g., leuprolide,

triptorelin, and histrelin implant) for the treatment of central precocious puberty.[8] GnRH agonists are generally well-tolerated in children and adolescents.

- **Prostate cancer:** The NCCN prostate cancer guidelines (version 1.2023 – September 16, 2022) list goserelin, leuprolide, and triptorelin as androgen deprivation therapy options for use in various settings: clinically localized disease, regional disease, prostate specific antigen persistence/recurrence after radical prostatectomy or external beam radiation therapy (castration-sensitive disease), and metastatic castration-sensitive disease.[9]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Supprelin LA, Vantas, and Zoladex. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vantas and Zoladex, as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated. Note that as with Supprelin LA, when Vantas is prescribed for central precocious puberty, it does not need to be prescribed by or in consultation with a specialist.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Supprelin LA is recommended in patients who meet the following criteria:

FDA-Approved Indication

1. **Central Precocious Puberty.** Approve for 1 year.

II. Coverage of Vantas is recommended in patients who meet one of the following criteria:

FDA-Approved Indication

1. **Prostate Cancer.** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

2. **Central Precocious Puberty.** Approve for 1 year.

III. Coverage of Zoladex is recommended in patients who meet one of the following criteria:

FDA-Approved Indications

1. **Abnormal Uterine Bleeding.** Approve Zoladex 3.6 mg for 2 months if the patient meets the following conditions (A and B):
   A) Zoladex is used as an endometrial-thinning agent prior to endometrial ablation; AND

B) The medication is prescribed by or in consultation with an obstetrician-gynecologist or a healthcare practitioner who specializes in the treatment of women's health.

2. **Breast Cancer**. Approve Zoladex 3.6 mg for 1 year if the patient meets the following conditions (A and B):
   A) Zoladex is used in a premenopausal or perimenopausal woman; AND
   B) The medication is prescribed by or in consultation with an oncologist.

3. **Endometriosis.** Approve Zoladex 3.6 mg for 6 months if the patient meets the following conditions (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) The medication is prescribed by or in consultation with an obstetrician-gynecologist or a healthcare practitioner who specializes in the treatment of women's health.

4. **Prostate Cancer**. Approve Zoladex 3.6 mg and/or 10.8 mg for 1 year if the medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Supprelin LA, Vantas, and Zoladex is not recommended in the following situations:

17. **Peripheral Precocious Puberty (also known as GnRH-independent precocious puberty)**. Children with peripheral precocious puberty do not respond to GnRH agonist therapy.[8] Treatment is directed at removing or blocking the production and/or response to the excess sex steroids, depending on the cause (e.g., surgically removing human chorionic gonadotropin-secreting tumors or using glucocorticoids to treat defects in adrenal steroidogenesis [such as classic congenital adrenal hyperplasia]).

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Gonadotropin-Releasing Hormone Agonists – Injectable Long-Acting Products Prior Authorization Policy
- Lupron Depot® (leuprolide acetate suspension for intramuscular injection – AbbVie)
- Lupaneta Pack® (leuprolide acetate for depot suspension; norethindrone acetate tablets co-packaged for intramuscular use and oral use, respectively – AbbVie) [discontinued]

REVIEW DATE: 02/22/2023

Overview

Lupaneta Pack is indicated for initial management of the painful symptoms of **endometriosis** and for management of recurrence of symptoms.[1,2] Lupaneta Pack was discontinued in 2021.

Lupron Depot (3.75 mg intramuscular (IM) injection every month, 11.25 mg IM injection every 3 months) is indicated for the following conditions:[3,4]
- Preoperative hematologic improvement of women with **anemia caused by uterine leiomyomata** (fibroids) for whom 3 months of hormonal suppression is deemed necessary. (Lupron Depot in combination with iron therapy).
- **Endometriosis**, including pain relief and reduction of endometriotic lesions (Lupron Depot monotherapy).
- **Endometriosis**, initial management of the painful symptoms of endometriosis and management of recurrence of symptoms (Lupron Depot in combination with norethindrone acetate 5 mg daily).

Lupron Depot (7.5 mg IM injection every month, 22.5 mg IM injection every 3 months, 30 mg IM injection every 4 months, and 45 mg IM injection every 6 months) is indicated for the **palliative treatment of advanced prostate cancer**.[5]

Duration of Treatment:
- Lupaneta Pack: Initial treatment course is limited to 6 months; a single retreatment course of up to 6 months is allowed. Total duration of treatment is limited to 12 months.[1,2]
- Lupron Depot 3.75 mg and 11.25 mg:[3,4]
    - Endometriosis: For the first 6 months of treatment, Lupron Depot may be used as monotherapy or in combination with norethindrone acetate. If retreatment is needed, Lupron Depot must be used in combination with norethindrone acetate (for 6 months). Total duration of treatment is limited to 12 months.
    - Uterine leiomyomata (fibroids): Recommended duration of treatment is up to 3 months.
- Lupron Depot 7.5 mg, 22.5 mg, 30 mg, and 45 mg: Labeling does not specify a treatment duration.

Guidelines

Abnormal Uterine Bleeding/Uterine Leiomyomata (Fibroids)

The American College of Obstetricians and Gynecologists (ACOG) [2021] practice bulletin regarding the management of symptomatic uterine leiomyomas discuss that gonadotropin-releasing hormone (GnRH) agonists (either with or without add-back hormonal therapy) are recommended for bleeding associated with fibroids, uterine enlargement associated with fibroids, and as a bridge to other treatment strategies (such as surgical management, menopause, or other medical therapies).[6] Add-back hormonal therapy (such as low-dose estrogen or progestin, or both), may help mitigate the hypoestrogenic effects of GnRH agonists, such

as decreased bone mineral density. The guidelines state that the type, dose, and route of delivery of add-back therapy depend on patient preference and the severity of symptoms.

GnRH agonists can also be used for acute abnormal uterine bleeding with an aromatase inhibitor or antagonist to prevent initial estrogen flare and for the treatment of heavy menstrual bleeding caused by leiomyoma-associated hormonal imbalance.[7] A clinical practice guideline from the Society of Obstetricians and Gynaecologists of Canada notes that leuprolide acetate or combined hormonal contraception should be considered highly effective in preventing abnormal uterine bleeding when initiated prior to cancer treatment in premenopausal women at risk of thrombocytopenia.[8] The ACOG committee opinion on options for prevention and management of menstrual bleeding in adolescent patients undergoing cancer treatment states that GnRH agonists are an option for menstrual suppression.[9]

Endometriosis

According to the ACOG practice bulletin on the management of endometriosis (2010, reaffirmed 2018), empiric therapy with a 3-month course of a GnRH agonist is appropriate after an appropriate pretreatment evaluation (to exclude other causes of chronic pelvic pain) and failure of initial treatment with oral contraceptives and nonsteroidal anti-inflammatory drugs (NSAIDs).[10] The ACOG committee opinion on dysmenorrhea and endometriosis in the adolescent (2018) notes that patients with endometriosis who have pain after conservative surgical therapy and suppressive hormonal therapy may benefit from at least 6 months of GnRH agonist therapy with add-back medicine.[11]

Other Uses With Supportive Evidence

The Endocrine Society Guideline (2017) for the Treatment of Gender-Dysphoric/Gender-Incongruent Persons note that persons who fulfill criteria for treatment and who request treatment should initially undergo treatment to suppress physical changes of puberty.[12] Pubertal hormonal suppression should typically be initiated after the adolescent first exhibits physical changes of puberty (Tanner stages G2/B2). However, there may be compelling reasons to initiate hormone treatment before the age of 16 years in some adolescents. The guidelines note suppression of pubertal development and gonadal function can be effectively achieved via gonadotropin suppression using GnRH analogs. Long-acting GnRH analogs are the currently preferred treatment option. An advantage to using a GnRH analog is that the effects can be reversed; pubertal suppression can be discontinued if the individual no longer wishes to transition. Upon discontinuation of therapy, spontaneous pubertal development has been shown to resume. The World Professional Association for Transgender Health (WPATH) Standards of Care (version 8) document also recommends the use of GnRH analogs to suppress endogenous sex hormones in transgender and gender diverse people for whom puberty blocking is indicated.[13] GnRH can also be used in patients during late puberty to suppress the hypothalamic-pituitary-gonadal axis to allow for lower doses of cross-sex hormones.[14] In addition to use in adolescents, GnRH analog therapy is also used in adults, particularly male-to-female patients.[15]

In addition to the approved indications, GnRH agonists such as long-acting leuprolide, have been used for other conditions. The National Comprehensive Cancer Network (NCCN) guidelines for Adolescent and Young Adult Oncology (version 3.2023 – January 9, 2023) note GnRH agonists may be used in (oncology) protocols that are predicted to cause prolonged thrombocytopenia and present a risk for menorrhagia.[16] There are some limited data on GnRH agonists to preserve ovarian function during chemotherapy and some have shown that GnRH agonists may be beneficial for fertility preservation, although the guidelines note further investigation is needed. The NCCN guidelines for Breast Cancer (version 2.2023 – February 7, 2023) note that luteinizing hormone-releasing hormone agonists, such as leuprolide, can be used for ovarian suppression.[17] The guidelines further note that randomized trials have shown that ovarian suppression with GnRH agonist therapy administered during adjuvant chemotherapy in premenopausal women with breast tumors (regardless of hormone receptor status) may preserve ovarian function and diminish the likelihood

of chemotherapy-induced amenorrhea. The NCCN guidelines for Head and Neck Cancer (version 1.2023 – December 20, 2022) note that a significant number of advanced salivary gland tumors with distant metastases are androgen receptor-positive (AR+), and therefore, the panel recommends patients with tumors that are AR+ receive androgen receptor therapy (i.e., leuprolide, bicalutamide).[18] The NCCN guidelines for Ovarian Cancer including Fallopian Tube Cancer and Primary Peritoneal Cancer (version 1.2023 – December 22, 2022) recommend leuprolide as a hormonal therapy option in various settings (e.g., primary therapy, adjuvant therapy, recurrence).[19]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lupaneta Pack and Lupron Depot. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lupaneta Pack and Lupron-Depot as well as the monitoring required for adverse events and long-term efficacy, approval for some of the conditions requires Lupaneta Pack or Lupron-Depot to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

Recommended Authorization Criteria

Coverage of Lupaneta Pack or Lupron Depot is recommended in those who meet one of the following criteria:

FDA-Approved Indications

23. Endometriosis. Approve Lupron Depot (3.75 mg or 11.25 mg) or Lupaneta Pack for 1 year if the patient has tried one of the following, unless contraindicated (A, B, or C):

A) A contraceptive (e.g., combination oral contraceptives, levonorgestrel-releasing intrauterine systems [e.g., Mirena, Liletta]), OR

B) An oral progesterone (e.g., norethindrone tablets), OR

C) A depo-medroxyprogesterone injection.

Note**:** An exception to the requirement for a trial of the above therapies can be made if the patient has previously used a gonadotropin-releasing hormone [GnRH] agonist (e.g., Lupron Depot) or antagonist (e.g., Orilissa).

24. Prostate Cancer. Approve Lupron Depot 7.5 mg, 22.5 mg, 30 mg, or 45 mg for 1 year if prescribed by or in consultation with an oncologist.

25. Uterine Leiomyomata (fibroids). Approve Lupron Depot 3.75 mg or 11.25 mg for 3 months.

Other Uses with Supportive Evidence

26. Abnormal Uterine Bleeding. Approve Lupron Depot 3.75 mg or 11.25 mg for 6 months.

27. Breast Cancer. Approve Lupron Depot 3.75 mg, or 11.25 mg for 1 year if prescribed by or in consultation with an oncologist.

28. Gender Dysphoric/Gender-Incongruent Person; Person Undergoing Gender Reassignment (Female-To-Male [FTM] or Male-To-Female [MTF]). Approve Lupron Depot for 1 year if

prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of transgender patients.

29. **Head and Neck Cancer – Salivary Gland Tumors.** Approve Lupron Depot 3.75 mg, 7.5 mg, 11.25mg, or 22.5 mg for 1 year if the patient meets the following criteria (A, B, and C):
    A) Patient has recurrent, unresectable, or metastatic disease; AND
    B) Patient has androgen receptor-positive disease; AND
    C) The medication is prescribed by or in consultation with an oncologist.

30. **Ovarian Cancer.** Approve Lupron Depot 3.75 mg, 7.5 mg, 11.25 mg, or 22.5 mg for 1 year if prescribed by or in consultation with an oncologist.

31. **Preservation of Ovarian Function/Fertility in Patients Undergoing Chemotherapy.** Approve Lupron Depot 3.75 mg or 11.25 mg for 1 year if prescribed by or in consultation with an oncologist.

32. **Prophylaxis or Treatment of Uterine Bleeding or Menstrual Suppression in Patients with Hematologic Malignancy, or Undergoing Cancer Treatment, or Prior to Bone Marrow/Stem Cell Transplantation (BMT/SCT).** Approve Lupron Depot 3.75 mg or 11.25 mg for 1 year if prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lupron Depot and Lupaneta Pack is not recommended in the following situations:

18. **Hirsutism.** The Endocrine Society guidelines on the treatment of hirsutism in premenopausal women (2018) suggest against using GnRH agonists except in women with severe forms of hyperandrogenemia, such as ovarian hyperthecosis, who have had a suboptimal response to oral contraceptives and antiandrogens.[20]

19. **Menstrual Migraine.** A review article notes that GnRH analogs are effective in eliminating menstrual migraines, but their use is limited due to the significant adverse effects of estrogen deficiency, including severe vasomotor symptoms, sleep disruption, and a marked reduction in bone density.[21,22]

20. **Premenstrual Syndrome (PMS).** On occasion, GnRH analogs are recommended as an aid in the diagnosis of PMS.[23] Use of GnRH analogs results in profound cycle suppression and elimination of PMS symptoms, but these agents should not be used routinely. GnRH analogs are recommended only as a third-line treatment or for the most refractory patients.

21. **Polycystic Ovarian Syndrome (PCOS).** Review articles[24,25] do not recommend GnRH agonists as a treatment modality for this diagnosis. Additionally, the International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome (2018) only mentions GnRH products as they relate to infertility and assisted reproductive technology procedures.[26]

22. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Gonadotropin-Releasing Hormone Antagonists – Myfembree Prior Authorization Policy
- Myfembree® (relugolix, estradiol, and norethindrone acetate tablets – Myovant)

REVIEW DATE: 04/26/2023

OVERVIEW

Myfembree, an oral gonadotropin-releasing hormone (GnRH) receptor antagonist with added estrogen and progestin therapy, is indicated for the following uses:[1]

- Management of heavy menstrual bleeding associated with **uterine leiomyomas (fibroids)** in premenopausal women.
- Management of moderate to severe pain associated with **endometriosis** in premenopausal women.

Limitation of Use. Use should be limited to 24 months due to the risk of continued bone loss which may not be reversible.[1]

Disease Overview

Uterine fibroids (leiomyomas) are benign tumors. They are the most frequent gynecologic benign disease.[2] Fibroids can be asymptomatic or cause symptoms; symptoms generally present as abnormal (heavy) uterine bleeding or pelvic pain/pressure. Heavy menstrual bleeding can cause associated problems, such as iron deficiency anemia. The actual prevalence of uterine fibroids is difficult to ascertain since many patients are asymptomatic, but it is estimated that fibroids can be detected in up to 80% of women by 50 years of age.[3]

Endometriosis is a condition where the tissues similar to the lining of the uterus (or endometrium) migrate outside of the womb to other body sites.[4,5] The migrated tissues are generally found in the pelvic cavity (e.g., peritoneum, uterosacral ligaments, rectal-vaginal septum, or any spaces between the bladder, uterus, vagina, and rectum) and can attach to any of the female reproductive organs (e.g., ovaries, fallopian tubes). The migrated tissue is less commonly found outside the pelvic cavity or on the intestines, colon, appendix or rectum. Endometriosis impacts up to 10% of patients of reproductive age in the US.[5]

Guidelines

Abnormal Uterine Bleeding/Uterine Leiomyomata (Fibroids)

Myfembree is addressed in the American College of Obstetrician and Gynecologists (ACOG) guidelines on the management of symptomatic uterine leiomyomas (2021) as a medication under clinical study (prior to FDA approval).[6] Medical treatment options for uterine leiomyomas include agents that address only bleeding symptoms, such as GnRH antagonists, levonorgestrel-releasing intrauterine devices, contraceptive steroids, and tranexamic acid. Agents that reduce both bleeding and leiomyoma size include GnRH agonists and selective progesterone receptor modulators (SPRMs). SPRMs are not approved in the US for the treatment of uterine leiomyomas. An oral GnRH antagonist, such as Oriahnn or Myfembree, can be considered for the treatment of abnormal uterine bleeding related to leiomyomas for up to 2 years. The hormonal add-back therapy is indicated to offset the hypoestrogenic effects of the product.

Endometriosis

According to the ACOG practice bulletin on the management of endometriosis (2010, reaffirmed 2018), empiric therapy with a 3-month course of a GnRH agonist is appropriate after an appropriate pretreatment

evaluation (to exclude other causes of chronic pelvic pain) and failure of initial treatment with oral contraceptives and nonsteroidal anti-inflammatory drugs (NSAIDs).[7]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Myfembree. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Myfembree as well as the monitoring required for adverse events and long-term efficacy, approval for certain diagnoses requires Myfembree to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Myfembree is recommended in those who meet one of the following criteria:

FDA-Approved Indications

35. Uterine Fibroids (Leiomyomas). Approve for up to 24 months if the patient meets the following criteria (A, B, C, D, E, F, and G):
Note: Approve for **up to** 24 months. For example, a patient who has already received 6 months of treatment with Myfembree should be approved for a duration of 18 months.
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient is PREmenopausal (before menopause); AND
- **C)** Patient is experiencing heavy menstrual bleeding associated with the uterine fibroids; AND
- **D)** Uterine fibroids have been confirmed by a pelvic ultrasound, including transvaginal ultrasonography or sonohysterography; hysteroscopy; or magnetic resonance imaging; AND
- **E)** Patient has tried at least one other therapy for the medical management of heavy menstrual bleeding; AND
  Note: Examples of therapy for the medical management of heavy menstrual bleeding include combination estrogen-progestin contraceptives (oral tablets, vaginal ring, transdermal patch), levonorgestrel-releasing intrauterine systems (e.g., Mirena, Liletta), oral progesterone (e.g., medroxyprogesterone acetate), depo-medroxyprogesterone injection, tranexamic acid tablets.
- **F)** Patient has not previously received a continuous regimen of 24 months or longer of therapy with Myfembree or Oriahnn; AND
- **G)** The medication is prescribed by or in consultation with an obstetrician-gynecologist or a health care practitioner who specializes in the treatment of women's health.

36. Endometriosis. Approve for up to 24 months if the patient meets the following criteria (A, B, and C):
Note: Approve for **up to** 24 months. For example, a patient who has already received 6 months of treatment with Myfembree should be approved for a duration of 18 months.
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient is PREmenopausal (before menopause); AND
- **C)** Patient has previously tried ONE of the following, unless contraindicated (i or ii):
  Note: An exception to this requirement can be made if the patient has previously used a gonadotropin-releasing hormone agonist (e.g., Lupron Depot [leuprolide depot injection]) or Orilissa (elagolix tablets).

i. A contraceptive (e.g., combination oral contraceptives, levonorgestrel-releasing intrauterine systems [e.g., Mirena {levonorgestrel intrauterine system}, Liletta {levonorgestrel intrauterine system}], depo-medroxyprogesterone injection); OR
ii. An oral progesterone (e.g., norethindrone tablets).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Myfembree is not recommended in the following situations:

74. Heavy Menstrual Bleeding not associated with Uterine Fibroids. Myfembree has shown efficacy in reducing heavy menstrual bleeding only in women with uterine fibroids.[1]

75. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Gonadotropin-Releasing Hormone Antagonists – Oriahnn Prior Authorization Policy
- Oriahnn™ (elagolix, estradiol, and norethindrone acetate capsules; elagolix capsules – AbbVie)

REVIEW DATE: 04/26/2023

OVERVIEW

Oriahnn, an oral gonadotropin-releasing hormone (GnRH) receptor antagonist with added estrogen and progestin therapy, is indicated for the **management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women**.[1] Limitation of Use: Use should be limited to 24 months due to the risk of continued bone loss which may not be reversible.[1]

Disease Overview

Uterine fibroids (leiomyomas) are benign tumors. They are the most frequent gynecologic benign disease.[2] Fibroids can be asymptomatic or cause symptoms; symptoms generally present as abnormal (heavy) uterine bleeding or pelvic pain/pressure. Heavy menstrual bleeding can cause associated problems, such as iron deficiency anemia. The actual prevalence of uterine fibroids is difficult to ascertain since many patients are asymptomatic, but it is estimated that fibroids can be detected in up to 80% of women by 50 years of age.[3]

Guidelines

Oriahnn is addressed in the American College of Obstetrician and Gynecologists guidelines on the management of symptomatic uterine leiomyomas (2021).[4] Medical treatment options for uterine leiomyomas include agents that address only bleeding symptoms, such as GnRH antagonists, levonorgestrel-releasing intrauterine devices, contraceptive steroids, and tranexamic acid. Agents that reduce both bleeding and leiomyoma size include GnRH agonists and selective progesterone receptor modulators (SPRMs). SPRMs are not approved in the U.S. for the treatment of uterine leiomyomas. An oral GnRH antagonist, such as Oriahnn or Myfembree, can be considered for the treatment of abnormal uterine bleeding related to leiomyomas for up to 2 years. The hormonal add-back therapy is indicated to offset the hypoestrogenic effects of the product.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Oriahnn. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Oriahnn as well as the monitoring required for adverse events and long-term efficacy, approval requires Oriahnn to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Oriahnn is recommended in those who meet the following criteria:

FDA-Approved Indication

37. Uterine Fibroids (Leiomyomas). Approve for up to 24 months if the patient meets the following criteria (A, B, C, D, E, F, and G):

Note: Approve for **up to** 24 months. For example, a patient who has already received 6 months of treatment with Oriahnn should be approved for a duration of 18 months.

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient is PREmenopausal (before menopause); AND
- **C)** Patient is experiencing heavy menstrual bleeding associated with the uterine fibroids; AND
- **D)** Uterine fibroids have been confirmed by a pelvic ultrasound, including transvaginal ultrasonography or sonohysterography; hysteroscopy; or magnetic resonance imaging; AND
- **E)** Patient has tried at least one other therapy for the medical management of heavy menstrual bleeding; AND

  Note: Examples of therapy for the medical management of heavy menstrual bleeding includes: combination estrogen-progestin contraceptives (oral tablets, vaginal ring, transdermal patch), levonorgestrel-releasing intrauterine systems [e.g. Mirena, Liletta], oral progesterone (e.g., medroxyprogesterone acetate), depo-medroxyprogesterone injection, tranexamic acid tablets.
- **F)** Patient has **not** previously received a continuous regimen of 24 months or longer of therapy with Oriahnn or Myfembree; AND
- **G)** The medication is prescribed by or in consultation with an obstetrician-gynecologist or a health care practitioner who specializes in the treatment of women's health.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Oriahnn is not recommended in the following situations:

76. Heavy Menstrual Bleeding not associated with Uterine Fibroids.
Oriahnn has been shown to be effective in reducing heavy menstrual bleeding only in women with uterine fibroids.[1]

77. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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345. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin. Management of Symptomatic Uterine Leiomyomas. June 2021. Available at: https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2021/06/management-of-symptomatic-uterine-leiomyomas. Accessed on April 20, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Gonadotropin-Releasing Hormone Antagonists – Orilissa Prior Authorization Policy
- Orilissa™ (elagolix tablets – AbbVie)

REVIEW DATE: 04/26/2023

OVERVIEW

Orilissa, an oral gonadotropin-releasing hormone (GnRH) receptor antagonist, is indicated for the management of moderate to severe pain associated with **endometriosis**.[1] Limitation of Use. Limit the duration of use based on the dose and coexisting condition.

The recommended dosage is 150 mg once daily (QD) for up to 24 months (no coexisting conditions) or 200 mg twice daily (BID) for up to 6 months (in patients with coexisting dyspareunia). In patients with moderate hepatic impairment (Child-Pugh Class B), the recommended dosage is 150 mg QD for up to 6 months and the use of 200 mg BID is not recommended. Orilissa is contraindicated in patients with severe hepatic impairment. Duration of therapy is limited due to the anti-estrogenic effects of the medication which include a decrease in bone mineral density.

Disease Overview

Endometriosis is a condition where the tissues similar to the lining of the uterus (or endometrium) migrate outside of the womb to other body sites.[2,3] The migrated tissues are generally found in the pelvic cavity (e.g., peritoneum, uterosacral ligaments, rectal-vaginal septum, or any spaces between the bladder, uterus, vagina, and rectum) and can attach to any of the female reproductive organs (e.g., ovaries, fallopian tubes). The migrated tissue is less commonly found outside the pelvic cavity or on the intestines, colon, appendix or rectum. Endometriosis impacts up to 10% of patients of reproductive age in the US.[3]

Guidelines

According to the American College of Obstetricians and Gynecologists practice bulletin on the management of endometriosis (2010, reaffirmed 2018), after an appropriate pretreatment evaluation (to exclude other causes of chronic pelvic pain) and failure of initial treatment with oral contraceptives and nonsteroidal anti-inflammatory drugs (NSAIDs), empiric therapy with a 3-month course of a GnRH agonist is appropriate.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Orilissa. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: When available, the ICD-10 codes for endometriosis (N80 through N80.9) **AND** a prior therapy in the last 180 days which includes any one of the following: contraceptives (STCs 0248, 9654, and 9495), intrauterine devices (STC 4730), oral progestins (STC 0246 RT 01), depo-medroxyprogesterone injections (STC 4139), GnRH agonists (STC 8253, STC E851, STC 8254 STR 0190 RT 27), Myfembree, or Orilissa will be used to allow approval of the requested medication.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Orilissa is recommended in those who meet the following criteria:

FDA-Approved Indication

36. Endometriosis. Approve for 6 months if the patient meets ONE of the following (A or B):

19. Initial Therapy. Approve if the patient has tried ONE of the following, unless contraindicated (i or ii):

Note: An exception to the requirement for a trial of the below therapies can be made if the patient had previously used a gonadotropin-releasing hormone agonist (e.g., Lupron Depot [leuprolide depot injection]) or Myfembree (relugolix, estradiol, norethindrone tablets) for endometriosis.

i. A contraceptive (e.g., combination oral contraceptives, levonorgestrel-releasing intrauterine systems [e.g., Mirena {levonorgestrel intrauterine system}, Liletta {levonorgestrel intrauterine system}], a depo-medroxyprogesterone injection); OR

ii. An oral progesterone (e.g., norethindrone tablets); OR

20. Patient is Currently Receiving Orilissa. Approve.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Orilissa is not recommended in the following situations:

23. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Gout – Krystexxa Prior Authorization Policy
- Krystexxa® (pegloticase intravenous infusion – Horizon)

REVIEW DATE: 05/17/2023

OVERVIEW

Krystexxa, a PEGylated uric acid specific enzyme, is indicated for treatment of **chronic gout refractory to conventional therapy**, in adult patients.[1] Krystexxa should be co-administered with methotrexate to increase effectiveness, prevent the formation of antibodies, and reduce infusion reactions. It is recommended that patients discontinue oral urate-lowering medications while on Krystexxa therapy due to the potential blunting of the rise of serum uric acid levels with concomitant use. Krystexxa has a Boxed Warning due to concerns for anaphylaxis and infusion reactions, and glucose-6-phosphate dehydrogenase (G6PD) deficiency associated hemolysis and methemoglobinemia.

Disease Overview

Gout is a form of inflammatory arthritis and results from a metabolic disorder called hyperuricemia caused by an overproduction or underexcretion of uric acid; however, asymptomatic patients with elevated uric acid levels do not have gout and do not require treatment.[2,3] Excessive amounts of uric acid in the blood lead to deposits of crystals in the joints and connective tissues and may cause excruciating pain. Lumps of urate crystals (tophi) may develop in soft tissues such as the elbow, ear, or distal finger joints. Some patients fail to normalize serum uric acid and have inadequate control of the signs and symptoms of gout with maximum medically appropriate doses or have a contraindication to urate-lowering therapies. Treatment-failure should be differentiated as those who are under-treated for gout or are non-compliant with gout therapy. Those with treatment-failure gout generally have a high prevalence of tophi, frequent and disabling gout flares, deforming arthropathy, diminished quality of life, and disability.

Guidelines

The American College of Rheumatology provides guidelines (2020) for the management of gout. Allopurinol is the preferred first-line urate-lowering therapy, including patients with moderate to severe gout.[3] Febuxostat and probenecid are conditionally recommended as alternative first-line therapies for specific patient populations. Titration of urate-lowering therapy should be guided by serum uric acid concentrations, with a target of < 6 mg/dL. In patients with refractory disease, effective therapeutic options include combination therapy with a xanthine oxidase inhibitor (e.g., allopurinol or febuxostat) and a uricosuric agent (e.g., probenecid, fenofibrate, or losartan). Krystexxa is not recommended as first-line therapy, however it is appropriate in patients with severe gout disease burden and refractoriness to, or intolerance of, appropriately dosed oral urate-lowering therapies.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Krystexxa. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Krystexxa as well as the monitoring required for adverse events and long-term efficacy, approval requires Krystexxa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Krystexxa is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Gout, Chronic.** Approve for the duration noted below if the patient meets ONE of the following conditions (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, and vi):
     - **i.** Patient meets one of the following conditions (a or b):
       - **a)** Patient has at least one tophus; OR
       - **b)** Patient has a of 2 previous flares in the past year (prior to the current flare); AND
     - **ii.** Patient meets one of the following conditions (a or b):
       - **a)** Patient had an inadequate response, defined as serum uric acid level that remained > 6 mg/dL following a 3-month trial of a xanthine oxidase inhibitor; OR
         Note: Examples of xanthine oxidase inhibitors include allopurinol and febuxostat.
       - **b)** Patient has a contraindication or has had an intolerance to a trial of allopurinol, as determined by the prescriber; AND
     - **iii.** Patient meets one of the following conditions (a or b):
       - **a)** Patient had an inadequate response, defined as serum uric acid level that remained > 6 mg/dL following a 3-month trial of a uricosuric agent; OR
         Note: Examples of uricosuric agents include probenecid, fenofibrate, and losartan.
       - **b)** According to the prescriber, the patient has renal insufficiency (e.g., decreased glomerular filtration rate); AND
     - **iv.** Krystexxa will be used in combination with ONE of the following (a, b, or c):
       - **a)** Methotrexate; OR
       - **b)** Leflunomide; OR
       - **c)** Azathioprine; AND
     - **v.** Krystexxa will not be used in combination with another uric acid lowering drug; AND
       Note: Examples of uric acid lower drugs include allopurinol, febuxostat, or probenecid.
     - **vi.** Krystexxa is prescribed by or in consultation with a rheumatologist or a nephrologist.
   - **B)** Patient is Currently Receiving Krystexxa. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, iv, and v):
     - **i.** Patient is continuing therapy with Krystexxa to maintain response/remission; AND
     - **ii.** Patient has responded to therapy with evidence of serum uric acid level < 6 mg/dL with continued Krystexxa treatments; AND
     - **iii.** Krystexxa is being used in combination with ONE of the following (a, b, or c):
       - **a)** Methotrexate; OR
       - **b)** Leflunomide; OR
       - **c)** Azathioprine; AND
     - **iv.** Krystexxa is not being used in combination with another uric acid lowering drug.
       Note: Examples of uric lower drugs include allopurinol, febuxostat, or probenecid.
     - **v.** Krystexxa is prescribed by or in consultation with a rheumatologist or a nephrologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Krystexxa is not recommended in the following situations:

78. Known Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency. Because of risks of hemolysis and methemoglobinemia, Krystexxa is contraindicated in G6PD deficiency.[1] Patients at increased risk of this deficiency (e.g., those of African or Mediterranean ancestry) should be screened prior to initiation of therapy.

79. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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347. Gout. Centers for Disease Control and Prevention [Web site]. Last reviewed July 27, 2020. Available at: http://www.cdc.gov/arthritis/basics/gout.html. Accessed on May 12, 2023.
348. FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American College of Rheumatology Guideline for the Management of Gout. *Arthritis Care Res*. 2020 Jun;72(6):744-760.

PRIOR AUTHORIZATION POLICY

POLICY: Growth Disorders – Growth Hormone Prior Authorization Policy
- Genotropin® (somatropin subcutaneous injection – Pfizer)
- Humatrope® (somatropin subcutaneous injection – Eli Lilly)
- Norditropin® (somatropin subcutaneous injection – Novo Nordisk)
- Nutropin AQ® (somatropin subcutaneous injection – Genentech)
- Omnitrope® (somatropin subcutaneous injection – Sandoz)
- Saizen® (somatropin subcutaneous injection – EMD Serono)
- Serostim® (somatropin subcutaneous injection – EMD Serono)
- Zomacton™ (somatropin subcutaneous injection – Ferring)
- Zorbtive® (somatropin injection – EMD Serono) [discontinued]

REVIEW DATE: 04/05/2023; selected revision 11/01/2023 (Effective for 1/1/2024)

OVERVIEW

Indications for somatropin vary among these products. Somatropin is indicated for the following uses:
- **Growth hormone deficiency (GHD) or failure**, treatment of pediatric patients, due to an inadequate secretion of endogenous growth hormone.[1-7]
- **Non-growth hormone deficient short stature (idiopathic short stature)**, treatment, defined by height standard deviation score (SDS) ≤ -2.25 , and associated with growth rates unlikely to permit attainment of adult height in the normal range.[1-4,6,7]
- **Adults with GHD** for replacement of endogenous growth hormone.[1-7]
- **Children with chronic kidney disease**, treatment of growth failure, up to the time of kidney transplantation.[4]
- **Noonan syndrome**, treatment of patients with short stature.[3]
- **Prader Willi syndrome**, treatment of patients with growth failure or short stature.[1,3,7]
- **Short stature homeobox-containing gene (SHOX) deficiency**, treatment of short stature or growth failure in children.[2,6]
- **Small for gestational age (SGA)**, treatment of growth failure or short stature in patients with no catch-up growth by age 2[1,7] to 4 years[2,3,6]
- **Turner syndrome**, treatment of short stature.[1-4,6,7]
- **Short bowel syndrome**, treatment, in adults receiving specialized nutritional support.[8]
- **Human immunodefiency virus (HIV)-infected patients with wasting or cachexia**, treatment, to increase lean body mass and body weight, and improve physical endurance.[9]

Growth Hormone Deficiency (GHD) in Children and Adolescents

Somatropin is indicated for the treatment of growth failure in children due to an inadequate secretion of endogenous growth hormone.[1-7] In these children with GHD, somatropin is effective for increasing final adult height.[31] Somatropin therapy is recommended to normalize adult height and avoid extreme shortness in children and adolescents with GHD.[31] Cranial radiation often causes hypopituitarism, and GHD is a frequent pituitary abnormality seen in children and adults who have undergone cranial radiation.[17] Children who have undergone total body irradiation in preparation for hematopoietic stem cell transplant commonly have GHD and an impaired growth rate; these patients can be treated successfully with growth hormone. Somatropin therapy improves the final height of young children after total body irradiation.[11]

Congenital Hypopituitarism

Somatropin is used in infants and young children with congenital hypopituitarism, that manifests in infancy with hypoglycemia, microgenitalia, hyperbilirubinemia, and multiple anterior pituitary hormone deficiencies.[31] The Pediatric Endocrine Society guidelines suggest that GHD due to congenital hypopituitarism be diagnosed without formal growth hormone provocative testing in a newborn with hypoglycemia who does not attain a serum growth hormone concentration > 5 mcg/L (> 5 ng/mL) and has deficiency of at least one additional pituitary hormone and/or the classical imaging triad (ectopic posterior pituitary and pituitary hypoplasia with abnormal stalk).[31]

(1) Non-Growth Hormone Deficient Short Stature (Idiopathic Short Stature) in Children or Adolescents

(2) Somatropin is indicated for the long-term treatment of idiopathic short stature (non-growth hormone deficient short stature) which is defined by a height standard deviation score (SDS) ≤ -2.25, and associated with growth rates that are unlikely to permit attainment of adult height in the normal range.[1-4,6,7] The predicted adult heights of these children are < 160 cm (63 inches) for men and < 150 cm (59 inches) in women.[31] The Pediatric Endocrine Society guidelines (2016) recommend that the decision to treat idiopathic short stature with somatropin be made on a case-by-case basis after assessing physical and psychological burdens, and discussion of risks and benefits.[31] They recommend against the routine use of somatropin in every child with height SDS ≤ -2.25. In one consensus statement on children with idiopathic short stature from the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop (2008), it was felt that the optimal age for initiating treatment is 5 years to early puberty.[12]

The initial 6-month trial of somatropin is to establish that the child's condition responds to somatropin therapy. Authorization for continued therapy should be based on an adequate clinical response defined as an annualized growth rate that doubles in comparison to the previous year.[14] Children who show a striking increase in growth velocity during the first 6 to 12 months of somatropin therapy are most likely to benefit from long-term therapy, and therapy should be discontinued if there is no significant increase in growth rate during the first year. Children who have a significant increase in growth rate after the first 6-month trial and the next 12 months should then be reviewed annually for growth rate, closure of the epiphyses, and/or attainment of mid-parental height.

(3)

(4) Growth Hormone Deficiency (GHD) in Adults or Transition Adolescents

Somatropin is indicated for the replacement of endogenous growth hormone in adults with GHD, which may present in adults or children as GHD (isolated GHD) or in addition to other pituitary hormone deficiencies (gonadotropin, adrenocorticotropic hormone, and/or thyroid-stimulating hormone deficiencies).[15] Patients with other anterior pituitary hormone deficiencies are likely to have GHD. In adults, the diagnosis of GHD usually is made in patients with signs and symptoms of hypothalamic-pituitary disease (endocrine, structural, and/or genetic causes); those who have received cranial irradiation or tumor treatment; or those with traumatic brain injury or subarachnoid hemorrhage.[15,16] Onset may be in adulthood or childhood. In childhood, the goal of somatropin therapy is primarily for statural growth. When final adult height is attained, somatropin therapy is no longer required for statural growth. Transition is used to describe the period in adolescence after growth is completed and the need for continued replacement into adulthood is assessed. Ongoing GHD is most likely in patients with multiple pituitary hormone deficits, with or without structural pituitary or peripituitary disease, and/or a history of cranial radiation therapy. Confirmatory growth hormone stimulation testing may not be required in patients, such as with congenital/genetic GHD or multiple pituitary hormone deficiencies. When persistent GHD is documented after completion of adult height, somatropin therapy should be continued to attain full skeletal and muscle maturation during the transition period from childhood to adulthood.[15] In adults with GHD, somatropin replacement therapy improves abnormalities in substrate metabolism, body composition, and physical and psychosocial function.[15,16]

Growth hormone is not approved by the FDA for the treatment of other conditions in adults who may have a low growth hormone response to growth hormone provocative testing (such as obesity, aging, or depression) or to improve athletic performance.[17,18]

Growth Hormone Stimulation Tests (Adults or Transition Adolescents)

The insulin tolerance test is the gold standard growth hormone stimulation test[53] but is contraindicated in patients with ischemic heart disease or seizure disorders or in elderly or pregnant patients.[15,16,27] The glucagon stimulation test and the macimorelin test could be considered as alternatives.[53] The response to all growth hormone stimulation tests show intra-individual variability, and the growth hormone cutoff points vary with the test used. Otherwise healthy obese persons have blunted growth hormone responses to various tests.[30] There is no information on the effects of increased body mass index (BMI) or central adiposity on the insulin tolerance test. When Geref (growth hormone releasing hormone) was available [discontinued in the US in 2008], Geref plus arginine was considered the best alternative to the insulin tolerance test in adults.

Macrilen (macimorelin oral solution) is the most recently approved test for the diagnosis of adult GHD. Patients in the pivotal trial were 18 to 66 years of age and the BMI ranged from 16 to 40 kg/m^2.[29] Safety and diagnostic performance have not been established in patients with BMI > 40 kg/m^2. Clinical studies established that a maximally stimulated serum growth hormone level of < 2.8 ng/mL (i.e., at the 30, 45, 60, and 90 minute time points) after Macrilen administration confirms the presence of adult GHD.

Arginine and levodopa testing have not been systematically evaluated and validated, and because they have a low sensitivity and specificity in adults and transition patients, it is not recommended to utilize these tests in this population.[53] Additionally, the clonidine, levodopa, and arginine alone tests are generally not recommended because very low growth hormone cutoff points are required to achieve adequate specificity.[27]

Adults with childhood onset GHD may have alterations in body composition, bone mineral density, and lipid metabolism that are alleviated by treatment with somatropin.[15,31] However, some children with a diagnosis of GHD have a normal somatotropic axis when retested in late adolescence.[31,52] Re-evaluation of the somatotropic axis in children diagnosed with GHD is required during the transition period. The transition period is the time from late puberty to establishment of adult muscle and bone composition, and encompasses attainment of adult height.[31] Re-evaluation of the somatotropic axis is most conveniently done when growth has slowed to the point where pediatric somatropin dosing will be discontinued (i.e., the growth velocity is < 2 to 2.5 cm/year). Recommendations for transitional care after childhood somatropin treatment from the Pediatric Endocrine Society guidelines[31] are as follows: Patients with multiple (≥ 3) pituitary hormone deficiencies regardless of etiology, or GHD with a documented causal genetic mutation or specific pituitary/hypothalamic structural defect (except ectopic posterior pituitary) be diagnosed with persistent GHD. These guidelines recommend re-evaluation of the somatotropic axis for persistent GHD in persons with 1) GHD and deficiency of only one additional pituitary hormone, 2) idiopathic isolated GHD, 3) idiopathic isolated GHD with or without a small pituitary/ectopic posterior pituitary, and 4) in patients after irradiation. Testing can be done after a trial of at least 1 month off somatropin treatment. The guidelines also recommend growth hormone provocative testing to evaluate the function of the somatotropic axis in the transition period if indicated by a low insulin-like growth factor (IGF)-1 level. Persons with idiopathic isolated GHD will very likely test sufficient with growth hormone provocative testing. To continue growth hormone therapy in adulthood, retesting for GHD with growth hormone stimulation test(s) is recommended in most transition patients and at least 1 month after discontinuation of pediatric growth hormone therapy.[53] Retesting is not required in transition patients with evidence of

panhypopituitarism (≥ 3 pituitary hormone deficiencies) and low serum IGF-1 levels, patients with genetic defects, and patients with hypothalamic-pituitary structural brain defects.

Adult GHD can be predicted with > 90% accuracy by the presence of three or four pituitary hormone deficiencies in addition to serum IGF-1 concentration that is less than the 2.5 percentile or < -2 SDS.[15,16] This is in the absence of conditions that lower IGF-1. Patients with ≥ 3 pituitary hormone deficiencies and an IGF-1 level below the reference range do not need a growth hormone stimulation test.[16] Because of the nature of the cause of GHD in children with structural lesions with multiple hormone deficiencies and those with proven genetic causes, provocative testing in these adults is not necessary.

Chronic Kidney Disease in Children or Adolescents

Somatropin is indicated for the treatment of growth failure in children with chronic kidney disease up to the time of kidney transplantation and is effective for increasing the rate of growth.[4] Somatropin therapy has increased final adult height in these patients.[19] An adequate growth response can be assumed if height velocity during the first year of growth hormone treatment is greater than 2 cm per year over baseline.[20] This increase is supported by outcomes of controlled trials specific to patients with chronic kidney disease. Guidelines recommend that persistent growth failure (defined as height below the third percentile and height velocity below the 25th percentile beyond a period of 3 months in infants or 6 months in children and adolescents), be an indication for growth hormone therapy once other potentially treatable risk factors for growth failure have been adequately addressed.[20] Growth hormone therapy can be initiated 1 year after transplantation if spontaneous catch-up growth does not occur and steroid-free immunosuppression is not a feasible option.

(5)

Noonan Syndrome and Short Stature in Children or Adolescents

Somatropin is indicated for the treatment of children with short stature associated with Noonan syndrome.[3,21] Not all patients with Noonan syndrome have short stature; some will achieve a normal adult height without treatment. The younger the age at start of therapy, the larger the change in height SDS.

Prader-Willi Syndrome

Somatropin is indicated for the treatment of pediatric patients who have growth failure due to Prader-Willi syndrome.[1,3,7] Somatropin therapy in children increases linear growth velocity, improves body composition (i.e., decreases the percentage body fat, increases or stabilizes lean body mass), increases bone mineral density, improves physical strength and agility, and improves final adult height.[22] After final height is attained, there may be potential benefits of somatropin on body composition, peak bone mass, cognition, and quality of life in adults.[22] Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment.[1,3,7] Confirmation of Prader-Willi requires molecular genetic testing for the identification of Prader-Willi genetic subtypes.[54]

Short Stature Homeobox-Containing Gene (SHOX) Deficiency in Children or Adolescents

(6) Somatropin is indicated for the treatment of short stature or growth failure in children with SHOX deficiency.[2,6] SHOX deficiency may result from either deletion of one copy of the *SHOX* gene or from mutation within or outside one copy of the *SHOX* gene that impairs the production or function of the SHOX protein. Women with Turner syndrome have only a single copy of the SHOX gene because they lack all or part of their second X chromosome.[23] SHOX deficiency is also the primary cause of short stature in most patients with Léri-Weill dyschondrosteosis (syndrome), and *SHOX* mutations and deletions are found in patients with idiopathic short stature. In one study consisting of a 2-year control period and a subsequent extension period to final height, short prepubertal patients with SHOX deficiency received somatropin.[24]

(7)

(8) Children Born Small for Gestational Age (SGA)

(9) Somatropin is indicated for the treatment of growth failure in children born SGA who fail to exhibit catch-up growth by age 2[1,7] to 4 years.[2,3,6] SGA is defined as a birth weight and/or birth length that is greater than 2 standard deviation (SD) [about the 3rd percentile] below mean normal values after adjusting for gestational age and sex. The terms SGA and intrauterine growth restriction are used interchangeably in this document. In clinical trials, patients born SGA (including children with Silver-Russell syndrome) without catch-up growth who were 2 to 11 years of age had significant increases in growth when treated with somatropin before puberty.[1,3] Optimal duration of therapy once catch-up growth has been attained is not known.
(10)
(11) Almost all patients with Silver-Russell syndrome are born SGA, and postnatal catch-up growth does not occur in the majority of children.[44] An expert consensus statement recommends that patients with Silver-Russell syndrome receive treatment with somatropin as soon as possible.[44] Starting therapy at age 2 to 4 years is adequate for the majority of patients. In some cases, somatropin therapy is started in patients less than 2 years of age who have severe fasting hypoglycemia, severe malnutrition, or severe muscular hypotonia. These experts recommend that somatropin therapy be stopped when height velocity is < 2 cm per year over a 6-month period and when bone age is > 14 years in females or > 17 years in males.
(12)

Turner Syndrome

Somatropin is indicated for the treatment of short stature associated with Turner syndrome.[1-4,6,7] Turner syndrome is a sex chromosome disorder caused by loss of part or all of an X chromosome; the diagnosis is confirmed by karyotype analysis. Growth hormone therapy is used to maximize adult height in these patients; there is no physiological rationale for continuing growth hormone into the transition period after the completion of puberty.[25]

Short Bowel Syndrome

Somatropin is indicated for the treatment of short bowel syndrome in adults receiving specialized nutritional support.[11]

Human Immunodeficiency Virus-Associated Wasting or Cachexia

Somatropin is indicated for the treatment of HIV-infected adults with wasting (loss of lean body mass) or cachexia to increase lean body mass and body weight, and improve physical endurance.[9] Somatropin therapy increases lean body mass, decreases fat mass, and increases physical function in patients with HIV-associated wasting. Studies directly comparing somatropin with other therapies (megestrol, oxandrolone, testosterone, and progressive resistance training) for wasting or cachexia in HIV-infection are lacking.[26]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of somatropin. All reviews will be directed to a clinician (i.e., pharmacist) for verification of criteria. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with somatropin as well as the monitoring required for adverse events and long-term efficacy, approval for some indications requires somatropin to be evaluated by a physician who specializes in the condition being treated. Human growth hormone is FDA-approved for treatment of a limited number of conditions. The FDA has not approved the use of human growth hormone as therapy for anti-aging, longevity, cosmetic uses, or performance enhancement. Federal law prohibits the dispensing of human growth hormone for non-approved purposes. A pharmacy's failure to comply with that law could result in significant criminal penalties to the pharmacy and its employees. Accordingly, a pharmacy may decline to dispense prescriptions for human growth hormone when written by physicians or other authorized prescribers who

they believe may be involved in or affiliated with the fields of anti-aging, longevity, rejuvenation, cosmetic uses, performance enhancement, or sports medicine.

Documentation: Documentation is required for use of somatropin as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information. For patient cases in which documentation is required, if this documentation has been previously received upon a prior coverage review, the documentation requirement is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Genotropin, Humatrope, Norditropin, Nutropin AQ, Omnitrope, Saizen, and Zomacton (all listed products except Serostim and Zorbtive) is recommended in those who meet at least ONE of the following criteria:

FDA-Approved Indications

1. **Growth Hormone Deficiency in a Child or Adolescent.** Approve for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial therapy. Approve if the patient meets at least ONE of the following (i, ii, iii, iv, or v):
     - **i.** Patient meets BOTH of the following (a and b):
       - **a)** Patient meets at least ONE of the following (1 or 2):
         - **(1)** Patient has had two growth hormone stimulation tests performed with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon AND the peak growth hormone response to both tests are < 10 ng/mL; OR
         - **(2)** Patient meets BOTH of the following (i and ii):
           - (i) Patient has had at least one growth hormone stimulation test performed with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon AND the peak growth hormone response to at least one test is < 10 ng/mL; AND
           - (ii) Patient has at least one risk factor for growth hormone deficiency; AND
             Note: Examples of at least one risk factor for growth hormone deficiency includes: the height for age curve has deviated downward across two major height percentiles [e.g., from above the 25th percentile to below the 10th percentile]; patient's growth rate is less than the expected normal growth rate based on age and gender; patient has low insulin-like growth factor (IGF)-1 and/or IGF binding protein-3 levels; patient has a very low peak growth hormone level on provocative testing as defined by the prescribing physician; patient's growth velocity is less than the 10th percentile for age and gender [height velocity percentile is NOT the same as height-for-age percentile]; patient is status post craniopharyngioma resection; patient has optic nerve hypoplasia; patient has a growth hormone gene deletion.
             Note: Some patients will achieve stimulated growth hormone concentrations in the normal range as determined by the testing laboratory and could be reviewed for authorization under non-growth hormone deficiency short stature (idiopathic short stature); AND
       - **b)** Patient has been evaluated by an endocrinologist; OR

ii. Patient has undergone brain radiation or tumor resection AND meets BOTH of the following (a and b):
- **a)** Patient meets at least ONE of the following (1 or 2):
  - **(1)** Patient meets BOTH of the following (i and ii):
    - (i) Patient has had one growth hormone stimulation test with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon; AND
    - (ii) The peak growth hormone response to at least one test is < 10 ng/mL; OR
  - **(2)** Patient has a deficiency in at least one other pituitary hormone (i.e., adrenocorticotropic hormone, thyroid-stimulating hormone, gonadotropin deficiency [luteinizing hormone and/or follicle stimulating hormone deficiency are counted as one deficiency], or prolactin); AND
- **b)** Patient has been evaluated by an endocrinologist; OR

iii. Patient has congenital hypopituitarism AND meets BOTH of the following (a and b):
- **a)** Patient meets at least ONE of the following (1, 2, or 3):
  - **(1)** Patient meets BOTH of the following (i and ii):
    - (i) Patient has had one growth hormone stimulation test with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon; AND
    - (ii) The peak growth hormone response to at least one test is < 10 ng/mL; OR
  - **(2)** Patient has a deficiency in at least one other pituitary hormone (i.e., adrenocorticotropic hormone, thyroid-stimulating hormone, gonadotropin deficiency [luteinizing hormone and/or follicle stimulating hormone deficiency are counted as one deficiency], or prolactin); OR
  - **(3)** Patient has the imaging triad of ectopic posterior pituitary and pituitary hypoplasia with abnormal pituitary stalk; AND
- **b)** Patient has been evaluated by an endocrinologist; OR

iv. Patient has multiple pituitary hormone deficiencies and meets BOTH of the following (a and b):

Note: Growth hormone deficiency may occur in combination with other pituitary hormone deficiencies and is referred to as hypopituitarism, panhypopituitarism, or multiple pituitary hormone deficiency.
- **a)** Patient meets at least ONE of the following (1 or 2):
  - **(1)** Patient has three or more of the following pituitary hormone deficiencies: somatropin (growth hormone), adrenocorticotropic hormone, thyroid-stimulating hormone, gonadotropin deficiency (luteinizing hormone and/or follicle stimulating hormone deficiency are counted as one deficiency), and prolactin; OR
  - **(2)** Patient meets BOTH of the following (i and ii):
    - (i) Patient has had one growth hormone stimulation test with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon; AND
    - (ii) The peak growth hormone response to at least one test is < 10 ng/mL; AND
- **b)** Patient has been evaluated by an endocrinologist; OR

v. Patient has had a hypophysectomy (surgical removal of pituitary gland).

B) Patient is continuing somatropin therapy (i.e., established on somatropin for ≥ 10 months). Approve if the patient meets at least ONE of the following (i, ii, or iii):

i. Patient is < 12 years of age. Patient's height has increased by ≥ 2 cm/year in the most recent year; OR

ii. Patient is between ≥ 12 years and < 18 years of age. Patient meets BOTH of the following (a and b):

a) Patient's height has increased by ≥ 2 cm/year in the most recent year; AND
b) Patient's epiphyses are open;OR

iii. Patient is ≥ 18 years of age. Patient meets ALL of the following (a, b, and c):
a) Patient's height has increased by ≥ 2 cm/year in the most recent year; AND
b) Patient's epiphyses are open; AND
c) Patient's mid-parental height has not been attained.
Note: Mid-parental height is the father's height plus the mother's height divided by 2, plus 2.5 inches if male or minus 2.5 inches if female.
Note: Adolescents and young adults with childhood onset growth hormone deficiency who have previously responded to somatropin with increases in height velocity and who have completed linear growth may continue receiving somatropin therapy as a transition adolescent or as an adult. See criteria I.3. (Growth hormone deficiency in an adult or transition adolescent).

2. Non-Growth Hormone Deficient Short Stature (Idiopathic Short Stature) in a Child or Adolescent. Approve for the duration noted if the patient meets at least ONE of the following (A or B):

A) Initial therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, and vi):
i. Patient is ≥ 5 years of age; AND
ii. Patient's baseline height is ≤ 1.2 percentile or a standard deviation score (SDS) ≤ -2.25 for age and gender; AND
iii. Patient's growth (height) velocity meets at least ONE of the following (a or b):
a) Patient has a growth rate < 4 cm/year; OR
b) Patient's growth (height) velocity is less than the 10th percentile for age and gender based on at least 6 months of growth data; AND
Note: Height velocity percentile is NOT the same as height for age percentile.
iv. Without growth hormone therapy, the patient's predicted adult height is < 160 cm (63 inches) in males or < 150 cm (59 inches) in females; AND
v. Patient's epiphyses are open; AND
vi. Patient does not have constitutional delay of growth and puberty.

B) Patient is continuing somatropin therapy. Approve for 1 year if the patient meets at least ONE of the following (i or ii):
i. Patient has received somatropin for ≥ 6 months and < 10 months. Approve if the patient meets BOTH of the following (a and b):
a) Patient is ≥ 5 years of age; AND
b) Patient's annualized growth rate has doubled in comparison to the previous year; OR
Note: For example, if the growth velocity was 3 cm/year for the year prior to treatment, then the growth velocity must be at least 3 cm in 6 months (baseline velocity was 1.5 cm/6 months) or for example, the growth velocity was 2 cm/year for the year prior to treatment, then after 6 months of somatropin therapy, the growth velocity must be at least 2 cm in 6 months (1 cm/6 months baseline).
ii. Patient has received somatropin for ≥ 10 months. Approve if the patient meets at least ONE of the following (a, b, or c):
a) Patient is ≥ 5 years and < 12 years of age. Patient's height has increased by ≥ 2 cm/year in the most recent year; OR
b) Patient is ≥ 12 years of age and < 18 years of age. Patient meets BOTH of the following (1 and 2):
(1) Patient's height has increased by ≥ 2 cm/year in the most recent year; AND
(2) Patient's epiphyses are open; OR

c) Patient is ≥ 18 years of age. Patient meets ALL of the following (1, 2, and 3):
- **(1)** Patient's height has increased by ≥ 2 cm/year in the most recent year; AND
- **(2)** Patient's epiphyses are open; AND
- **(3)** Patient's mid-parental height has not been attained.
  Note: Mid-parental height is the father's height plus the mother's height divided by 2, plus 2.5 inches if male or minus 2.5 inches if female.

3. Growth Hormone Deficiency in an Adult or Transition Adolescent. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) The endocrinologist must certify that somatropin is not being prescribed for anti-aging therapy or to enhance athletic ability or for body building; AND

B) Patient must have a diagnosis of growth hormone deficiency that is ONE of the following (i or ii): **[documentation required for all elements]**
- **i.** Childhood onset; OR
- **ii.** Adult onset that results from one of the following: growth hormone deficiency alone or multiple hormone deficiencies (hypopituitarism) resulting from pituitary disease, hypothalamic disease, pituitary surgery, cranial radiation therapy, tumor treatment, traumatic brain injury, or subarachnoid hemorrhage; AND

C) Patient meets at least ONE of the following (i, ii, or iii):
- **i.** Patient (adult or transition adolescent) has known perinatal insults OR congenital or genetic defects; **[documentation required]** OR
- **ii.** Patient meets ALL of the following (a, b, and c):
  - **a)** Patient (adult onset or transition adolescent) has three or more of the following pituitary hormone deficiencies: Adrenocorticotropic hormone , thyroid-stimulation hormone, gonadotropin deficiency (luteinizing hormone and/or follicle stimulating hormone deficiency are counted as one deficiency), and prolactin **[documentation required]**; AND
  - **b)** The age and gender adjusted serum insulin-like growth factor-1 is below the lower limit of the normal reference range for the reporting laboratory **[documentation required]**; AND
  - **c)** Other causes of low serum insulin-like growth factor-1 have been excluded (e.g., malnutrition, prolonged fasting, poorly controlled diabetes mellitus, hypothyroidism, hepatic insufficiency, oral estrogen therapy); OR
- **iii.** Patient meets at least ONE of the following (a or b):
  - **a)** Adult. Patient has had a negative response to at least ONE of the following standard growth hormone stimulation tests (1, 2, 3, 4, 5, or 6) **[documentation required for all elements]**:
    Note: If the patient has had a previous trial of an arginine test with a peak response of ≤ 0.4 mcg/L, this would meet the criteria for a negative response to a growth hormone stimulation test.
    - **(1)** Insulin tolerance test (obtaining at least 3 growth hormone levels in at least a 60 minute timeframe [not including a level at timeframe zero], with adequate hypoglycemia being achieved) with peak response ≤ 5.0 mcg/L; OR
    - **(2)** Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with peak response ≤ 3.0 mcg/L AND the patient's body mass index (BMI) is < 25 kg/m^2; OR
    - **(3)** Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with a peak response ≤ 3.0 mcg/L AND the patient's BMI is ≥ 25 kg/m^2 and ≤ 30 kg/m^2 with, according to the prescriber, a high pretest probability of growth hormone deficiency; OR
    - **(4)** Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with a peak response ≤ 1.0

mcg/L AND the patient's BMI is ≥ 25 kg/m^2 and ≤ 30 kg/m^2 with, according to the prescriber, a low pretest probability of growth hormone deficiency; OR

(5) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with peak response ≤ 1.0 mcg/L AND the patient's BMI is > 30 kg/m^2; OR

(6) Macrilen (macimorelin oral solution) test (obtaining at least 4 growth hormone levels in at least a 90 minute timeframe [not including a level at timeframe zero]) with peak responses < 2.8 ng/mL (2.8 mcg/L) AND the patient's BMI is ≤ 40 kg/m^2.
Note: The following formula can be used to calculate BMI: BMI equals body weight in kg divided by height meters squared (m^2) [i.e., BMI = kg/m^2]; OR

b) Transition adolescent. Patient meets BOTH of the following (1 and 2): **[documentation required for all elements]**:
Note: The transition period is the time from late puberty to establishment of adult muscle and bone composition, and encompasses attainment of adult height.
Note: If the patient has had a trial of a Macrilen test with a peak response of < 2.8 ng/mL (mcg/L), this would meet the criteria for a negative response to a growth hormone stimulation test.

(1) Patient has been off somatropin therapy for at least 1 month before retesting with a growth hormone stimulation test; AND

(2) Patient meets at least ONE of the following responses to growth hormone stimulation testing (i, ii, iii, iv, v or vi):

(i) Insulin tolerance test (obtaining at least 3 growth hormone levels in at least a 60 minute timeframe [not including a level at timeframe zero], with adequate hypoglycemia being achieved) with peak response ≤ 5.0 mcg/L; OR

(ii) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with peak response ≤ 3.0 mcg/L AND the patient's body mass index (BMI) is < 25 kg/m^2; OR

(iii) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with a peak response of ≤ 3.0 mcg/L AND the patient's BMI is ≥ 25 kg/m^2 and ≤ 30 kg/m^2 with, according to the prescriber, a high pretest probability of growth hormone deficiency; OR

(iv) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with a peak response ≤ 1.0 mcg/L AND the patient's BMI is ≥ 25 kg/m^2 and ≤ 30 kg/m^2 with, according to the prescriber, a low pretest probability of growth hormone deficiency; OR

(v) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with peak response ≤ 1.0 mcg/L AND the patient's BMI is > 30 kg/m^2; OR

(vi) If both the insulin tolerance test AND glucagon stimulation test are contraindicated, the arginine test can be used (obtaining at least 3 growth hormone levels in at least 120 minute timeframe [not including a level at timeframe zero]) with a peak response ≤ 0.4 mcg/L; AND

D) Patient has been evaluated by an endocrinologist.

4. Chronic Kidney Disease in a Child or Adolescent. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient has or had chronic kidney disease as defined by a glomerular filtration rate < 60 milliliters/minute; AND

B) Patient meets at least ONE of the following (i or ii):

i. Initial therapy. Approve if the patient meets BOTH of the following (a and b):

a) Patient has persistent growth failure as defined as BOTH of the following (1 and 2):

(1) Patient's baseline height is less than the 5th percentile for age and gender; AND

(2) Patient's baseline height velocity is below the 25th percentile over a period of 3 months in infants (≤ 1 year of age) or 6 months in children and adolescents; AND

b) Patient has been evaluated by an endocrinologist or a nephrologist; OR

ii. Patient is continuing somatropin therapy (i.e., established on somatropin for ≥ 10 months). Approve if the patient meets BOTH of the following (a and b):

a) Patient's height has increased by ≥ 2 cm/year in the most recent year; AND

b) Patient's epiphyses are open.

5. Noonan Syndrome in a Child or Adolescent. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) The diagnosis of Noonan syndrome has been confirmed by ONE of the following (i or ii):

i. Noonan syndrome has been confirmed with genetic testing; OR

ii. If genetic testing does not definitively confirm the diagnosis, the prescriber has made a clinical diagnosis of Noonan syndrome: AND

Note: Clinical diagnosis includes abnormal facial features (high forehead, epicanthic folds, etc.), pulmonary valve stenosis and/or hypertrophic cardiomyopathy, first-degree relative with Noonan syndrome, mild developmental delay.

B) Patient meets at least ONE of the following (i or ii):

i. Initial therapy. Approve if the patient meets BOTH of the following (a and b):

a) Patient's baseline height is less than the 5th percentile using a growth chart for children without Noonan syndrome; AND

b) Patient has been evaluated by an endocrinologist; OR

ii. Patient is continuing somatropin therapy (i.e., established on somatropin for ≥ 10 months). Approve if the patient meets BOTH of the following (a and b):

a) Patient's height has increased by ≥ 2 cm/year in the most recent year; AND

b) Patient's epiphyses are open.

6. Prader-Willi Syndrome. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) The diagnosis of Prader-Willi syndrome has been confirmed by genetic testing; AND

B) Patient meets at least ONE of the following (i or ii):

i. Initial therapy. Approve if the patient (child or adult) has been evaluated by an endocrinologist; OR

ii. Patient is continuing somatropin therapy (i.e., established on somatropin for ≥ 10 months). Approve if the patient meets at least ONE of the following (a or b):

a) Child or adolescent. The patient meets BOTH of the following (1 and 2):

(1) Patient's height has increased by ≥ 2 cm/year in the most recent year; AND

(2) Patient's epiphyses are open; OR

Note: When the epiphyses are closed and/or the height velocity is < 2 cm/year, the patient can be reviewed for continuation of therapy as an adult with Prader-Willi syndrome.

b) Adult or adolescent whose epiphyses are closed and/or whose height velocity is < 2 cm/year. Patient meets BOTH of the following (1 and 2):

(1) This physician must certify that somatropin is not being used for anti-aging therapy or to enhance athletic performance/body building; AND

(2) Patient must be evaluated by an endocrinologist or in consultation with an endocrinologist.

7. **Short Stature Homeobox-Containing Gene Deficiency in a Child or Adolescent.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient has short stature homeobox-containing gene deficiency demonstrated by chromosome analysis; AND
   B) Patients meets at least ONE of the following (i or ii):
      i. Initial therapy. Approve if the patient meets ALL of the following (a, b, and c):
         a) Patient's epiphyses are open; AND
         b) Patient's baseline height is less than the 5th percentile for age and gender; AND
         c) Patient has been evaluated by an endocrinologist;OR
      ii. Patient is continuing somatropin therapy (i.e., established on somatropin for ≥ 10 months). Approve if the patient meets BOTH of the following (a and b):
         a) Patient's height has increased by ≥ 2 cm/year in the most recent year; AND
         b) Patient's epiphyses are open.

8. **Child Born Small for Gestational Age or with Intrauterine Growth Restriction Including a Child with Silver-Russell Syndrome.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient meets BOTH of the following (i and ii):
      i. Patient was born small for gestational age, which is defined as birth weight and/or birth length that is > 2 standard deviations (SD) below the mean (< -2 SD) for gestational age and gender; AND
      ii. Patient did not have sufficient catch-up growth before age 2 to 4 years; AND
   B) Patient meets at least ONE of the following (i or ii):
      i. Initial therapy. Approve if the patient meets ALL of the following (a, b, and c):
         a) Patient is ≥ 2 years of age; AND
         b) Patient's baseline height is less than the 5th percentile for age and gender; AND
         c) Patient has been evaluated by an endocrinologist; OR
      ii. Patient is continuing somatropin therapy (i.e., established on somatropin for ≥ 10 months). Approve if the patient meets at least ONE of the following (a or b):
         a) Patient is < 12 years of age. Patient's height has increased by ≥ 2 cm/year in the most recent year; OR
         b) Patient is ≥ 12 years. Patient meets BOTH of the following (1 and 2):
            (1) Patient's height has increased by ≥ 2 cm/year in the most recent year; AND
            (2) Patient's epiphyses are open.

9. **Turner Syndrome**. Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) The diagnosis of Turner's syndrome has been confirmed by karyotype analysis (i.e., chromosome analysis); AND
   B) Patient meets at least ONE of the following (i or ii):
      i. Initial therapy. Patient's baseline height is less than the 5th percentile for age and gender; OR
      ii. Patient is continuing somatropin therapy (i.e., established on somatropin for ≥ 10 months). Approve if the patient meets BOTH of the following (a and b):
         a) Patient's height has increased by ≥ 2 cm/year in the most recent year; AND
         b) Patient's epiphyses are open.

II. Coverage of Genotropin, Humatrope, Norditropin, Nutropin AQ, Omnitrope, Saizen, Zomacton, and Zorbtive (all listed products except Serostim) is recommended in patients who meet the following criteria:

1. **Short Bowel Syndrome in an Adult**. Approve for 1 month if the patient meets at least ONE of the following (A or B):
   - **A)** Initial therapy. Approve if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient is receiving specialized nutritional support (defined as a high carbohydrate, low-fat diet that is adjusted for individual patient requirements and preferences); AND
     - **iii.** Patient is dependent on intravenous parenteral nutrition.
   - **B)** Patient is continuing somatropin therapy. Approve if the adult patient responded to somatropin therapy with a decrease in the requirement for specialized nutritional support according to the prescriber.

III. Coverage of Serostim is recommended in those who meet the following criteria:

1. **Human Immunodeficiency Virus Infection with Wasting or Cachexia in an Adult.** Approve for 6 months if the patient meets ALL of the following (A, B, C, D, E, F, and G):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets at least ONE of the following (i, ii, or iii):
     - **i.** Documented unintentional weight loss of ≥ 10% from baseline; OR
     - **ii.** Patient's weight < 90% of the lower limit of ideal body weight; OR
     - **iii.** Patient's body mass index (BMI) ≤ 20 kg/m^2; AND
       Note: The following formula can be used to calculate BMI: BMI equals body weight in kg divided by height in meters squared (m^2) [i.e., BMI = kg/m^2].
   - **C)** Patient has wasting or cachexia that is due to malabsorption, poor diet, opportunistic infection, or depression, and other causes have been addressed prior to starting somatropin; AND
   - **D)** Patient has been on antiretroviral therapy or highly active antiretroviral treatment for ≥ 30 days prior to beginning Serostim therapy and will continue antiretroviral therapy throughout the course of Serostim treatment; AND
   - **E)** Serostim is not being used solely for treatment of alterations in body fat distribution such as increased abdominal girth, lipodystrophy and excess abdominal fat, or buffalo hump; AND
   - **F)** Patient meets at least ONE of the following (i or ii):
     - **i.** Patient has tried one appetite stimulant or other anabolic agent; OR
       Note: Examples of appetite stimulants or other anabolic agents include megestrol acetate, dronabinol, oxandrolone.
     - **ii.** Appetite stimulants or other anabolic agents are contraindicated; AND
   - **G)** If the patient has previously received treatment with Serostim for this use, patient has been off Serostim therapy for at least 1 month.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Genotropin, Humatrope, Norditropin, Nutropin AQ, Omnitrope, Saizen, Zomacton, Serostim, and Zorbtive is not recommended in the following situations:

Note: For some of the following indications, authorization for coverage is not recommended because the indication is excluded from coverage in a typical pharmacy benefit.

1. **Acute Critical Illness Due to Complications Following Surgery, Multiple Accidental Trauma, or with Acute Respiratory Failure.**[1-9] In two placebo-controlled trials in non-growth hormone deficient adults (n = 522) with these conditions, there was a significant increase in mortality (42% vs. 19%) in patients treated with somatropin compared to those on placebo.

2. **Aging (i.e., Anti-Aging), to Improve Functional Status in an Elderly Patient, and Somatopause.**[17,18,32,33] Somatropin is not FDA-approved for anti-aging therapy, to improve functional status in elderly patients, or to treat somatopause. Federal law prohibits the distribution or dispensing of somatropin for non-FDA approved uses. There are no long-term studies assessing somatropin efficacy and safety for anti-aging therapy. Short-term therapy with somatropin may improve some measures of body composition, including increased muscle mass, reduced total body fat, improved skin elasticity, and reduced rate of bone demineralization, but somatotropin does not have positive effects on strength, functional capacity, or metabolism. Somatropin is associated with considerable adverse effects in non-growth hormone deficient adults (e.g., carpal tunnel syndrome, soft tissue edema, arthralgias, glucose intolerance, increased serum lipids). Another concern is the possible increased risk of cancer with long-term use of somatropin and the potentiating effects of IGFs on cancer. Somatropin is not indicated for the age-related decrease in growth hormone/IGF-1 status.[16]

3. **Athletic Ability Enhancement.**[18,34] Somatropin is not FDA-approved for athletic performance enhancement or for body building in nonathletes. Federal law prohibits the distribution or dispensing of somatropin for non-FDA approved uses. Short-term administration of somatropin to increase strength and endurance in athletes is no more effective than training alone and somatropin should not be administered to athletes or other persons for the purpose of enhancing athletic ability or improving personal appearance (i.e., to appear leaner and more muscular). Somatropin has been used in supraphysiologic doses alone or in combination with other performance enhancing drugs (PEDs) in users who are not athletes.[34] Use of PEDs has been linked to an increased risk of death and many adverse effects including cardiovascular, psychiatric, metabolic, endocrine, neurologic, infectious, hepatic, renal, and musculoskeletal disorders.

4. **Central Precocious Puberty.** Children with precocious puberty are often treated with gonadotropin releasing hormone (GnRH) agonists (Lupron® [leuprolide acetate injection]) to suppress pituitary gonadal activity, to slow the advancement of bone age (prevent premature fusion of the epiphyseal growth plates), and to improve adult height. In some patients GnRH agonist therapy may result in marked deceleration of bone growth and may result in adult height that is less than the mid-parental height. Somatropin has been used in girls when growth velocity decreases or if it appears that the targeted adult height will not be attained.[35] There are no large well-controlled trials on the efficacy and safety of adding somatropin to GnRH agonist therapy in these children or the effect on final height.[35,36]

5. **Chronic Fatigue Syndrome.** There is no evidence of GHD in chronic fatigue syndrome.[37]

6. **Congenital Adrenal Hyperplasia (CAH).**[38,39] The Endocrine Society clinical practice guidelines on CAH due to steroid 21-hydroxylase deficiency recommend against the use of experimental treatment approaches outside of formally approved clinical trials.[39] Children with predicted adult height SD $\leq$ -2.25 may be considered for growth-promoting treatments in appropriately controlled trials.

7. **Constitutional Delay of Growth and Puberty.** These children have delayed skeletal maturation and pubertal development. Administering somatropin does not increase adult height (which is usually normal).[40] Short-term androgen therapy accelerates growth and the rate of pubertal advancement in boys.

8. **Corticosteroid-Induced Short Stature.**[13] This includes a variety of chronic glucocorticoid-dependent conditions, such as asthma, Crohn's disease,[13] juvenile rheumatoid arthritis,[28,41,42] as well as after renal, heart, liver, or bone marrow transplantation.[43] Short-term improvement in growth velocity in children with glucocorticoid-induced suppression has been reported with somatropin therapy. Long-term data are not available.[13] Children being considered for treatment with somatropin should be enrolled in studies that allow careful monitoring and data analysis.

9. **Fibromyalgia.** In one placebo-controlled study, 120 non-GHD adult women with severe fibromyalgia and low levels of IGF-1 were randomized to somatropin 0.006 mg/kg/day for 12 months (dose was adjusted) or placebo for 6 months.[45] Patients receiving placebo initially were switched to somatropin from Months 6 to 12 (open label). Standard therapy for fibromyalgia was continued. After 6 months, there were no differences between somatropin and placebo in the percentage of patients with fewer than 11 positive tender points, mean number of tender points, intensity of pain in every point evaluated, and other measures. After 12 months of somatropin therapy, 53% of patients had less than 11 positive tender points compared with 33% of patients who received placebo and then somatropin for 6 months ($P < 0.05$). At 18 months follow-up evaluation when somatropin was discontinued, impairment in pain perception worsened in both groups but to a lesser extent in the patients on somatropin for 12 months. Further controlled trials with a longer duration,[46] with different doses, and using the 2010 American College of Rheumatology criteria for fibromyalgia are needed. Some patients with fibromyalgia may have adult GHD.

10. **Human Immunodeficiency Virus (HIV)-Infected Patient with Alterations in Body Fat Distribution** (e.g., increased abdominal girth, lipodystrophy and excess abdominal fat, buffalo hump).[26] Somatropin is not indicated for the treatment of HIV-associated adipose redistribution syndrome (HARS). HARS is a subset of HIV lipodystrophy and is defined as maldistribution of body fat characterized by central fat accumulation (lipohypertrophy) with or without lipoatrophy. In HARS, fat may also accumulate in the upper body subcutaneous area such as the dorsocervical area (buffalo hump). These changes may be associated with metabolic disturbances (insulin resistance, glucose intolerance, dyslipidemia) and belly image distress. Safety and efficacy are not established.

11. **Infertility.**[47,10] Clinical trials indicate that somatropin is not useful as an adjunct during in vitro fertilization, for induction of ovulation in polycystic ovary syndrome, or for assisted reproductive technology. The authors of a recent meta-analysis concluded there is no evidence of an increased chance of a live birth with use of somatropin.

12. **Obesity.**[48,49] Somatropin is not indicated for the treatment of obesity. Low growth hormone levels are a consequence of central obesity and not a cause. Obesity is associated with decreased basal and pusatile release of growth hormone and decreased stimulated growth hormone release. Somatropin therapy does not have significant beneficial effects on obesity in persons without GHD and does not produce significant overall weight loss. Supraphysiologic doses of somatropin have been used to treat obesity. Effects of long-term therapy with somatropin are unknown.

13. **Osteoporosis.**[50,51] Guidelines for treatment or prevention of osteoporosis do not include recommendations for use of somatropin. In one double-blind trial, 80 postmenopausal women with

osteoporosis (56% of patients [n = 45/80] had a of fractures) were randomized to somatropin 0.33 mg/day or 0.83 mg/day or to placebo for three years.[50] The double-blind phase was 18 months and patients on somatropin continued drug for another 18 months and patients on placebo stopped at 18 months. Patients were compared with an age-matched random population sample of women (n = 120). All patients received calcium 750 mg, vitamin D 400 units, and hormone replacement therapy. All women were followed for a total of 10 years. Bone mineral density (BMD) increased in the patients receiving somatropin at Years 4 and 5, and after 10 years, BMD decreased to similar levels as before treatment. At 10 years, 28% of women (n = 22/80) had fractures. In the control group, fractures increased from 8% of patients at baseline to 32% of patients after 10 years. At 10 years, 41% of patients (n = 33/80) had stopped hormone replacement therapy; 23% had started bisphosphonates due to fractures, and 3% had received Forteo® (teriparatide injection). Larger studies are needed to determine the effects of somatropin therapy on bone mineral density and fractures in non-growth hormone deficient persons.

14. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Growth Disorders – Increlex Prior Authorization Policy
- Increlex® (mecasermin [rDNA origin] subcutaneous injection – Ipsen)

REVIEW DATE: 12/13/2023

OVERVIEW

Increlex, an insulin-like growth factor (IGF-1), is indicated for the treatment of growth failure in pediatric patients ≥ 2 years of age with the following conditions:[1]

- **Primary IGF-1 deficiency**, for patients with severe disease, defined as:
  - Height standard deviation score ≤ -3.0; AND
  - Basal IGF-1 standard deviation score ≤ -3.0; AND
  - Normal or elevated growth hormone level.
- **Growth hormone gene deletion**, in patients who have developed neutralizing antibodies to growth hormone.

Increlex is given by subcutaneous injection twice daily, shortly before or after a meal or snack. Treatment with Increlex should continue until the epiphyses fuse indicating full growth potential has been achieved.[2] It is a limitation of use that Increlex is not a substitute to growth hormone for approved growth hormone indications. Increlex is not indicated in secondary forms of IGF-1 deficiency, such as growth hormone deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory corticosteroids.[1]

15.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Increlex. Because of the specialized skills required for evaluation and diagnosis of patients treated with Increlex as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Increlex to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Increlex is recommended in those who meet one of the following criteria:

FDA-Approved Indications

33. Insulin-Like Growth Factor-1 (IGF-1) Deficiency – Severe, Primary Disease. Approve for 1 year if the patient meets ONE of the following conditions (A or B):

A) Initial Therapy or Patient Has Been on Increlex < 1 Year. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, iv, v, vi, and vii):
- **i.** Patient is ≥ 2 years of age; AND
- **ii.** The epiphyses are open; AND
- **iii.** Height standard deviation score is ≤ -3.0 at baseline; AND
- **iv.** Basal IGF-1 standard deviation score is ≤ -3.0 at baseline; AND

Note: Baseline is prior to initiation of treatment with Increlex. Reference ranges for IGF-1 vary among laboratories and are dependent upon age, gender, and puberty status.

v. Growth hormone concentration is normal or increased at baseline; AND

vi. Patient will not be receiving concurrent treatment with growth hormone; AND

vii. The medication is prescribed by or in consultation with a pediatric endocrinologist.

B) Patient Has Been Receiving Increlex for ≥ 1 Year. Approve if the patient meets ALL of the following (i, ii, and iii):

i. Patient's height has increased by ≥ 2 cm/year in the most recent year; AND

ii. The epiphyses are open; AND

iii. Patient will not be receiving concurrent treatment with growth hormone.

34. Growth Hormone Gene Deletion. Approve for 1 year if the patient meets ONE of the following conditions (A or B):

A) Initial Therapy or Patient Has Been on Increlex < 1 Year. Approve if the patient meets ALL of the following (i, ii, iii, iv, and v):

i. Patient is ≥ 2 years of age; AND

ii. The epiphyses are open; AND

iii. Patient has developed neutralizing antibodies to growth hormone; AND

iv. Patient will not be receiving concurrent treatment with growth hormone; AND

v. The medication is prescribed by or in consultation with a pediatric endocrinologist.

B) Patient Has Been Receiving Increlex for ≥ 1 Year. Approve if the patient meets ALL of the following (i, ii, iii, and iv):

i. Patient's height has increased by ≥ 2 cm/year in the most recent year; AND

ii. The epiphyses are open; AND

iii. Patient has developed neutralizing antibodies to growth hormone; AND

iv. Patient will not be receiving concurrent treatment with growth hormone.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Increlex is not recommended in the following situations:

1. Idiopathic Short Stature. Increlex has not been fully evaluated for this indication. Small studies have suggested some patients may respond to IGF-1 therapy[3]; however, patients with idiopathic short stature also respond to somatropin. Somatropin (monotherapy) is indicated for idiopathic short stature[4] and there is insufficient evidence to determine the risks and benefits of Increlex for this indication.

2. Growth Hormone Deficiency. Increlex is not a substitute to somatropin for approved somatropin uses and is not indicated for use in patients with secondary forms of IGF-1 deficiency, such as growth hormone deficiency.[1]

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Growth Disorders – Ngenla Prior Authorization Policy
- Ngenla® (somatrogon-ghla subcutaneous injection – Pfizer)

REVIEW DATE: 07/26/2023; selected revision 11/01/2023

OVERVIEW

Ngenla, a human growth hormone (hGH) product, is indicated for the treatment **growth failure due to inadequate secretion of growth hormone (GH)** in pediatric patients ≥ 3 years of age.[1]

Disease Overview

Ngenla is a hGH analog which is made up of the amino acid sequence of hGH with an added three copies of the C-terminal peptide of human chorionic gonadotropin.[1] The addition of the C-terminal peptides lead to a longer half-life. Ngenla binds to the GH receptor which initiates changes in growth and metabolism. In children with GH deficiency (GHD), somatropin is effective for increasing final adult height.[2] Somatropin therapy is recommended to normalize adult height and prevent extreme shortness in children and adolescents with GHD.[2] In addition to congenital causes, hypopituitarism may also be caused by radiation therapy; somatropin may be used to improve final height of children who have undergone radiation.[3,4]

Guidelines

Current guidelines do not specifically address Ngenla. Neither the Pediatric Endocrine Society guidelines for children and adolescents with GHD[2] (2016) nor the GH Research Society guidelines on children with short stature[11] (2019) recommend a specific GH product for GHD. Guidelines recommend the use of GH to normalize adult height and prevent extreme shortness in pediatric patients with GHD.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ngenla. All reviews will be directed to a clinician (i.e., pharmacist) for verification of criteria. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ngenla as well as monitoring required for adverse events and long-term efficacy, initial approval requires the patient to be evaluated by a physician who specializes in the condition being treated. hGH is FDA-approved for treatment of a limited number of conditions. The FDA has not approved the use of hGH as therapy for anti-aging, longevity, or cosmetic or performance enhancement. Federal law prohibits the dispensing of hGH for non-approved purposes. A pharmacy's failure to comply with that law could result in significant criminal penalties to the pharmacy and its employees. Accordingly, a pharmacy may decline to dispense prescriptions for hGH when written by a physician or other authorized prescribers who they believe may be involved in or affiliated with the fields of anti-aging, longevity, rejuvenation, cosmetic, performance enhancement, or sports medicine.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Ngenla is recommended in those who meet the following criteria:

FDA-Approved Indication

38. Growth Hormone Deficiency in a Pediatric Patient (≥ 3 years of age to < 18 years of age). Approve for 1 year if the patient meets the following (A or B):

A) Initial Therapy with any Growth Hormone Agent. Approve if the patient meets one of the following (i, ii, iii, iv, or v):

i. Patient meets BOTH of the following a (a and b):

a) Patient meets at least ONE of the following (1 or 2):

(1) Patient has had two growth hormone stimulation tests performed with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon AND the peak growth hormone response to both tests are < 10 ng/mL; OR

(2) Patient meets BOTH of the following (a and b):

(i) Patient has had at least one growth hormone stimulation test performed with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon AND the peak growth hormone response to at least one test is < 10 ng/mL; AND

(ii) Patient has at least one risk factor for growth hormone deficiency (e.g., the height for age curve has deviated downward across two major height percentiles [e.g., from above the 25th percentile to below the 10th percentile]; the child's growth rate is less than the expected normal growth rate based on age and gender; low insulin-like growth factor [IGF]-1 and/or IGFBP-3 levels; the child has a very low peak growth hormone level on provocative testing as defined by the prescribing physician; the child's growth velocity is less than the 10th percentile for age and gender [height velocity percentile is NOT the same as height-for-age percentile]; the patient is status post craniopharyngioma resection; the patient has optic nerve hypoplasia; the patient has a growth hormone gene deletion); AND

b) Patient has been evaluated by an endocrinologist.

ii. Patient has undergone brain radiation or tumor resection AND meets BOTH of the following (a and b):

a) Patient meets at least ONE of the following (1 or 2):

(1) Patient meets BOTH of the following (i and ii):

(i) Patient has had one growth hormone stimulation test with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon; AND

(ii) The peak growth hormone response to at least one test is < 10 ng/mL; OR

(2) Patient has a deficiency in at least one other pituitary hormone (i.e., adrenocorticotropic hormone, thyroid-stimulating hormone, gonadotropin [luteinizing hormone and/or follicle stimulating hormone deficiency are counted as one deficiency], or prolactin); AND

b) Patient has been evaluated by an endocrinologist.

iii. Patient has congenital hypopituitarism AND meets BOTH of the following (a and b):

a) Patient meets at least ONE of the following (1, 2, or 3):

(1) Patient meets BOTH of the following (i and ii):

(i) Patient has had one growth hormone stimulation test with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon; AND

(ii) The peak growth hormone response to at least one test is < 10 ng/mL; OR

(2) Patient has a deficiency in at least one other pituitary hormone (i.e., adrenocorticotropic hormone, thyroid-stimulating hormone, gonadotropin [luteinizing hormone and/or follicle stimulating hormone deficiency are counted as one deficiency], or prolactin); OR

(3) Patient has the imaging triad of ectopic posterior pituitary and pituitary hypoplasia with abnormal pituitary stalk; AND

b) Patient has been evaluated by an endocrinologist.

iv. Patient has multiple pituitary hormone deficiencies and meets BOTH of the following (a and b):

16. Note: Growth hormone deficiency may occur in combination with other pituitary hormone deficiencies and is referred to as hypopituitarism, panhypopituitarism, or multiple pituitary hormone deficiency.

a) Patient meets at least ONE of the following (1 or 2):

(1) Patient has three or more of the following pituitary hormone deficiencies: somatropin (growth hormone), adrenocorticotropic hormone, thyroid-stimulating hormone, gonadotropin (luteinizing hormone and/or follicle stimulating hormone deficiency are counted as one deficiency), and prolactin; OR

(2) Patient meets BOTH of the following (i and ii):

(i) Patient has had one growth hormone stimulation test with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon; AND

(ii) The peak growth hormone response to at least one test is < 10 ng/mL; AND

b) Patient has been evaluated by an endocrinologist.

v. Patient has had a hypophysectomy (surgical removal of pituitary gland).

B) Patient is Currently Receiving Ngenla or is switching to Ngenla from another Growth Hormone Agent (Patient has been established on either therapy for ≥ 10 months). Approve if the patient meets one of the following (i or ii):

i. Patient is < 12 years of age: Patient's height has increased by ≥ 2 cm/year in the most recent year; OR

ii. Patient is ≥ 12 years of age and < 18 years of age: Patient meets both of the following (a and b):

a) Patient's height has increased by ≥ 2 cm/year in the most recent year; AND

b) Patient's epiphyses are open.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ngenla is not recommended in the following situations:

80. Athletic Ability Enhancement.[5] Somatropin and related agents are not FDA-approved for athletic performance enhancement or for body building in non-athletes. Federal law prohibits the distribution or dispensing of somatropin or related agents for non-FDA approved uses.

81. Central Precocious Puberty. Children with precocious puberty are often treated with gonadotropin releasing hormone (GnRH) agonists (Lupron® [leuprolide acetate injection]) to suppress pituitary gonadal activity, to slow the advancement of bone age (prevent premature fusion of the epiphyseal growth plates), and to improve adult height. In some patients, GnRH agonist therapy may result in marked deceleration of bone growth and may result in adult height that is less than the midparental height. Somatropin has been used in girls when growth velocity decreases or if it appears that the targeted adult height will not be attained.[6] There are no large well-controlled trials on the efficacy and safety of adding somatropin to GnRH agonist therapy in these children or the effect on final height.[6,7]

82. Congenital Adrenal Hyperplasia (CAH).[8,9] The Endocrine Society clinical practice guidelines on CAH due to steroid 21-hydroxylase deficiency recommend against the use of experimental treatment approaches outside of formally approved clinical trials.[9] Children with predicted adult height standard deviation ≤ -2.25 may be considered for growth-promoting treatments in appropriately controlled trials.

83. Constitutional Delay of Growth and Puberty. These children have delayed skeletal maturation and pubertal development. Administering somatropin does not increase adult height (which is usually normal).[10] Short-term androgen therapy accelerates growth and the rate of pubertal advancement in boys.

17.

84. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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18.

PRIOR AUTHORIZATION POLICY

POLICY: Growth Disorders – Skytrofa Prior Authorization Policy
- Skytrofa™ (lonapegsomatropin subcutaneous injection – Ascendis Pharma)

REVIEW DATE: 05/31/2023; selected revision 11/01/2023

OVERVIEW

Skytrofa, a weekly human growth hormone (GH) product, is indicated for the treatment of pediatric patients ≥ 1 year of age who weigh at least 11.5 kg and have **growth failure due to an inadequate secretion of endogenous growth hormone**.[1]

Disease Overview

Lonapegsomatropin is a prodrug of somatropin.[1] In children with GH deficiency (GHD), somatropin is effective for increasing final adult height.[2] Somatropin therapy is recommended to normalize adult height and avoid extreme shortness in children and adolescents with GHD.[2] In addition to congenital causes, hypopituitarism may also be caused by radiation therapy; somatropin may be used to improve final height of children who have undergone radiation.[3,4]

Guidelines

Current guidelines do not specifically address Skytrofa. Neither the Pediatric Endocrine Society guidelines for children and adolescents with GH deficiency[2] (2016) nor the GH Research Society guidelines on children with short stature[11] (2019) recommend a specific GH product for GH deficiency. Guidelines recommend the use of GH to normalize adult height and avoid extreme shortness in pediatric patients with GHD.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Skytrofa. All reviews will be directed to a clinician (i.e., pharmacist) for verification of criteria. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Skytrofa as well as monitoring required for adverse events and long-term efficacy, initial approval requires the patient to be evaluated by a physician who specializes in the condition being treated. Human growth hormone is FDA-approved for treatment of a limited number of conditions. The FDA has not approved the use of human growth hormone as therapy for anti-aging, longevity, cosmetic or performance enhancement. Federal law prohibits the dispensing of human growth hormone for non-approved purposes. A pharmacy's failure to comply with that law could result in significant criminal penalties to the pharmacy and its employees. Accordingly, a pharmacy may decline to dispense prescriptions for human growth hormone when written by a physician or other authorized prescribers who they believe may be involved in or affiliated with the fields of anti-aging, longevity, rejuvenation, cosmetic, performance enhancement, or sports medicine.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Skytrofa is recommended in those who meet the following criteria:

FDA-Approved Indication

39. Growth Hormone Deficiency in a Pediatric Patient (≥ 1 year of age to < 18 years of age). Approve for 1 year if the patient meets the following (A or B):

B) Initial Therapy with any Growth Hormone Agent. Approve if the patient meets one of the following (i, ii, iii, iv, or v):

i. Patient meets BOTH of the following criteria (a and b):

a) Patient meets at least ONE of the following criteria (1 or 2):

(1) Patient has had two growth hormone stimulation tests performed with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon AND the peak growth hormone response to both tests are < 10 ng/mL; OR

(2) Patient meets BOTH of the following criteria (a and b):

(i) Patient has had at least one growth hormone stimulation test performed with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon AND the peak growth hormone response to at least one test is < 10 ng/mL; AND

(ii) Patient has at least one risk factor for growth hormone deficiency (e.g., the height for age curve has deviated downward across two major height percentiles [e.g., from above the 25th percentile to below the 10th percentile]; the child's growth rate is less than the expected normal growth rate based on age and gender; low insulin-like growth factor (IGF)-1 and/or IGFBP-3 levels; the child has a very low peak growth hormone level on provocative testing as defined by the prescribing physician; the child's growth velocity is less than the 10th percentile for age and gender [height velocity percentile is NOT the same as height-for-age percentile]; the patient is status post craniopharyngioma resection; the patient has optic nerve hypoplasia; the patient has a growth hormone gene deletion); AND

b) Patient has been evaluated by an endocrinologist.

ii. Patient has undergone brain radiation or tumor resection AND meets BOTH of the following criteria (a and b):

a) Patient meets at least ONE of the following (1 or 2):

(1) Patient meets BOTH of the following (i and ii):

(iii) Patient has had one growth hormone stimulation test with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon; AND

(iv) The peak growth hormone response to at least one test is < 10 ng/mL; OR

(2) Patient has a deficiency in at least one other pituitary hormone (i.e., adrenocorticotropic hormone, thyroid-stimulating hormone, gonadotropin [luteinizing hormone and/or follicle stimulating hormone deficiency are counted as one deficiency], or prolactin); AND

b) Patient has been evaluated by an endocrinologist.

iii. Patient has congenital hypopituitarism AND meets BOTH of the following (a and b):

a) Patient meets at least ONE of the following (1, 2, or 3):

(1) Patient meets BOTH of the following (i and ii):

(iii) Patient has had one growth hormone stimulation test with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon; AND

(iv) The peak growth hormone response to at least one test is < 10 ng/mL; OR

(2) Patient has a deficiency in at least one other pituitary hormone (i.e., adrenocorticotropic hormone, thyroid-stimulating hormone, gonadotropin [luteinizing hormone and/or follicle stimulating hormone deficiency are counted as one deficiency], or prolactin); OR

(3) Patient has the imaging triad of ectopic posterior pituitary and pituitary hypoplasia with abnormal pituitary stalk; AND

b) Patient has been evaluated by an endocrinologist.

iv. Patient has multiple pituitary hormone deficiencies and meets BOTH of the following (a and b):

19. Note: Growth hormone deficiency may occur in combination with other pituitary hormone deficiencies and is referred to as hypopituitarism, panhypopituitarism, or multiple pituitary hormone deficiency.

a) Patient meets at least ONE of the following criteria (1 or 2):

(1) Patient has three or more of the following pituitary hormone deficiencies: somatropin (growth hormone), adrenocorticotropic hormone, thyroid-stimulating hormone, gonadotropin (luteinizing hormone and/or follicle stimulating hormone deficiency are counted as one deficiency), and prolactin; OR

(2) Patient meets BOTH of the following criteria (i and ii):

(j) Patient has had one growth hormone stimulation test with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon; AND

(ii) The peak growth hormone response to at least one test is < 10 ng/mL; AND

b) Patient has been evaluated by an endocrinologist.

v. Patient has had a hypophysectomy (surgical removal of pituitary gland).

C) Patient is Currently Receiving Skytrofa or is switching to Skytrofa from another Growth Hormone Agent (Patient has been established on either therapy for ≥ 10 months). Approve if the patient meets one of the following (i or ii):

i. Patient is < 12 years of age: Patient's height has increased by ≥ 2 cm/year in the most recent year; OR

ii. Patient is ≥ 12 years of age and < 18 years of age: Patient meets both of the following (a and b):

a) Patient's height has increased by ≥ 2 cm/year in the most recent year; AND

b) Patient's epiphyses are open.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Skytrofa is not recommended in the following situations:

85. Athletic Ability Enhancement.[5] Somatropin and related agents are not FDA-approved for athletic performance enhancement or for body building in non-athletes. Federal law prohibits the distribution or dispensing of somatropin or related agents for non-FDA approved uses.

86. Central Precocious Puberty. Children with precocious puberty are often treated with gonadotropin releasing hormone (GnRH) agonists (Lupron® [leuprolide acetate injection]) to suppress pituitary gonadal activity, to slow the advancement of bone age (prevent premature fusion of the epiphyseal growth plates), and to improve adult height. In some patients, GnRH agonist therapy may result in marked deceleration of bone growth and may result in adult height that is less than the midparental height. Somatropin has been used in girls when growth velocity decreases or if it appears that the targeted adult height will not be attained.[6] There are no large well-controlled trials on the efficacy and safety of adding somatropin to GnRH agonist therapy in these children or the effect on final height.[6,7]

87. **Congenital Adrenal Hyperplasia (CAH).**[8,9] The Endocrine Society clinical practice guidelines on CAH due to steroid 21-hydroxylase deficiency recommend against the use of experimental treatment approaches outside of formally approved clinical trials.[9] Children with predicted adult height standard deviation ≤ -2.25 may be considered for growth-promoting treatments in appropriately controlled trials.

88. **Constitutional Delay of Growth and Puberty.** These children have delayed skeletal maturation and pubertal development. Administering somatropin does not increase adult height (which is usually normal).[10] Short-term androgen therapy accelerates growth and the rate of pubertal advancement in boys.

20.

89. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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21.

PRIOR AUTHORIZATION POLICY

POLICY: Growth Disorders – Sogroya Prior Authorization Policy
- Sogroya® (somapacitan-beco subcutaneous injection – Novo Nordisk)

REVIEW DATE: 05/31/2023; selected revision 11/01/2023

OVERVIEW

Sogroya, a long-acting human growth hormone (hGH) analog, is indicated for the treatment of pediatric patients ≥ 2.5 years of age who have growth failure due to inadequate secretion of growth hormone (GH).[1] Sogroya is also indicated for the replacement of endogenous GH in adults with GH deficiency (GHD).

Disease Overview

GHD in Children and Adolescents

Sogroya is a hGH analog.[1] In children with GHD, somatropin is effective for increasing final adult height.[2] Somatropin therapy is recommended to normalize adult height and avoid extreme shortness in children and adolescents with GHD.[2] In addition to congenital causes, hypopituitarism may also be caused by radiation therapy; somatropin may be used to improve final height of children who have undergone radiation.[3,4]

GHD in Adults or Transition Adolescents

Somatropin is indicated for the replacement of endogenous GH in adults with GH, which may present in adults or children as GHD.[11] Patients with other anterior pituitary hormone deficiencies are likely to have GHD. In adults, the diagnosis of GHD usually is made in patients with signs and symptoms of hypothalamic-pituitary disease (endocrine, structural, and/or genetic causes); those who have received cranial irradiation or tumor treatment; or those with traumatic brain injury or subarachnoid hemorrhage.[11,12] Onset may be in adulthood or childhood. In childhood, the goal of somatropin therapy is primarily for statural growth. When final adult height is attained, somatropin therapy is no longer required for statural growth. Transition is used to describe the period in adolescence after growth is completed and the need for continued replacement into adulthood is assessed. Confirmatory GH stimulation testing may not be required in patients, such as those with congenital/genetic GHD or multiple pituitary hormone deficiencies. When persistent GHD is documented after completion of adult height, somatropin therapy should be continued to attain full skeletal and muscle maturation during the transition period from childhood to adulthood.[11] In adults with GHD, somatropin replacement therapy improves abnormalities in substrate metabolism, body composition, and physical and psychosocial function.[11,12] GH is not approved by the FDA for the treatment of other conditions in adults who may have a low GH response to GH provocative testing (such as obesity, aging, or depression) or to improve athletic performance.[13,14]

Guidelines

Current guidelines do not specifically address Sogroya. Neither the Pediatric Endocrine Society guidelines for children and adolescents with GH deficiency[2] (2016) nor the GH Research Society guidelines on children with short stature[15] (2019) recommend a specific GH product for GHD. Both publications note that newer long-acting GH preparations may reduce the frequency of injections. The American Association of Clinical Endocrinologists and the American College of Endocrinology guidelines for management of GHD in adults and patients transitioning from pediatric to adult care[16] (2019) also do not prefer one GH agent over another. These guidelines state that when the clinician is suspicious of adult GHD, establishing a diagnosis is essential before replacement with GH. Adult GHD is associated with numerous adverse metabolic abnormalities (abdominal obesity, reduced lean body mass, increased peripheral insulin

resistance, impaired cardiac performance) which may contribute to increased cardiovascular morbidity and mortality.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Sogroya. All reviews will be directed to a clinician (i.e., pharmacist) for verification of criteria. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sogroya as well as monitoring required for adverse events and long-term efficacy, initial approval requires the patient to be evaluated by a physician who specializes in the condition being treated. Human growth hormone is FDA-approved for treatment of a limited number of conditions. The FDA has not approved the use of human growth hormone as therapy for anti-aging, longevity, cosmetic or performance enhancement. Federal law prohibits the dispensing of human growth hormone for non-approved purposes. A pharmacy's failure to comply with that law could result in significant criminal penalties to the pharmacy and its employees. Accordingly, a pharmacy may decline to dispense prescriptions for human growth hormone when written by a physician or other authorized prescribers who they believe may be involved in or affiliated with the fields of anti-aging, longevity, rejuvenation, cosmetic, performance enhancement, or sports medicine.

Documentation: Documentation is required for use of Sogroya as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information. For patient cases in which documentation is required, if this documentation has been previously received upon a prior coverage review, the documentation requirement is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sogroya is recommended in those who meet the following criteria:

FDA-Approved Indication

40. Growth Hormone Deficiency in a Child or Adolescent (≥ 2.5 years of age). Approve for 1 year if the patient meets ONE the following (A or B):

C) Initial Therapy with any Growth Hormone Agent. Approve if the patient meets ONE of the following (i, ii, iii, iv, or v):

i. Patient meets BOTH of the following (a and b):

a) Patient meets ONE of the following (1 or 2):

(1) Patient has had two growth hormone stimulation tests performed with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon AND the peak growth hormone response to both tests are < 10 ng/mL; OR

(2) Patient meets BOTH of the following criteria (i and ii):

(v) Patient has had at least one growth hormone stimulation test performed with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon AND the peak growth hormone response to at least one test is < 10 ng/mL; AND

(vi) Patient has at least one risk factor for growth hormone deficiency; AND

1. Note: Examples of at least one risk factor for growth hormone deficiency includes: the height for age curve has deviated downward across two major height

percentiles (e.g., from above the 25th percentile to below the 10th percentile); the child's growth rate is less than the expected normal growth rate based on age and gender; low insulin-like growth factor (IGF)-1 and/or IGFBP-3 levels; the child has a very low peak growth hormone level on provocative testing as defined by the prescribing physician; the child's growth velocity is less than the 10th percentile for age and gender (height velocity percentile is NOT the same as height-for-age percentile); the patient is status post craniopharyngioma resection; the patient has optic nerve hypoplasia; the patient has a growth hormone gene deletion; AND

b) Patient has been evaluated by an endocrinologist.

ii. Patient has undergone brain radiation or tumor resection AND meets BOTH of the following (a and b):

a) Patient meets at least ONE of the following (1 or 2):

(1) Patient meets BOTH of the following (i and ii):

(i) Patient has had at least one growth hormone stimulation test performed with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon; AND

(ii) The peak growth hormone response to at least one test is < 10 ng/mL; OR

(2) Patient has a deficiency in at least one other pituitary hormone (i.e., adrenocorticotropic hormone, thyroid-stimulating hormone, gonadotropin [luteinizing hormone and/or follicle stimulating hormone deficiency are counted as one deficiency], or prolactin); AND

b) Patient has been evaluated by an endocrinologist.

iii. Patient has congenital hypopituitarism AND meets BOTH of the following (a and b):

a) Patient meets at least ONE of the following (1, 2, or 3):

(1) Patient meets BOTH of the following (i and ii):

(i) Patient has had at least one growth hormone stimulation test performed with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon; AND

(ii) The peak growth hormone response to at least one test is < 10 ng/mL; OR

(2) Patient has a deficiency in at least one other pituitary hormone (i.e., adrenocorticotropic hormone, thyroid-stimulating hormone, gonadotropin [luteinizing hormone and/or follicle stimulating hormone deficiency are counted as one deficiency], or prolactin); OR

(3) Patient has the imaging triad of ectopic posterior pituitary and pituitary hypoplasia with abnormal pituitary stalk; AND

b) Patient has been evaluated by an endocrinologist.

iv. Patient has multiple pituitary hormone deficiencies and meets BOTH of the following (a and b):

2. Note: Growth hormone deficiency may occur in combination with other pituitary hormone deficiencies and is referred to as hypopituitarism, panhypopituitarism, or multiple pituitary hormone deficiency.

a) Patient meets at least ONE of the following (1 or 2):

(1) Patient has three or more of the following pituitary hormone deficiencies: somatropin (growth hormone), adrenocorticotropic hormone, thyroid-stimulating hormone, gonadotropin (luteinizing hormone and/or follicle stimulating hormone deficiency are counted as one deficiency), and prolactin; OR

(2) Patient meets BOTH of the following (i and ii)

(i) Patient had one growth hormone stimulation test with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon; AND

(ii) The peak growth hormone response to at least one test is < 10 ng/mL; AND

b) Patient has been evaluated by an endocrinologist.

v. Patient has had a hypophysectomy (surgical removal of pituitary gland).

B) Patient is Currently Receiving Sogroya or is switching to Sogroya from another Growth Hormone Agent (Patient has been established on either therapy for ≥ 10 months). Approve if the patient meets one of the following (i, ii, or iii):

i. Patient is < 12 years of age: Patient's height has increased by ≥ 2 cm/year in the most recent year; OR

ii. Patient is ≥ 12 years of age and < 18 years of age: Patient meets both of the following (a and b):

a) Patient's height has increased by ≥ 2 cm/year in the most recent year; AND

b) Patient's epiphyses are open.

iii. Patient is ≥ 18 years of age. Patient meets ALL of the following (a, b, and c):

a) Patient's height has increased by ≥ 2 cm/year in the most recent year; AND

b) Patient's epiphyses are open; AND

c) Mid-parental height has not been attained.

Note: Mid-parental height is the father's height plus the mother's height divided by 2, plus 2.5 inches if male or minus 2.5 inches if female.

Note: Adolescents and young adults with childhood onset growth hormone deficiency who have completed linear growth may continue receiving Sogroya therapy as a transition adolescent or as an adult. See criteria for Growth Hormone Deficiency in an adult or transition adolescent.

2. Growth Hormone Deficiency in an Adult or Transition Adolescent. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) The endocrinologist must certify that growth hormone therapy is not being prescribed for anti-aging therapy or to enhance athletic ability or for body building; AND

B) Patient must have a diagnosis of growth hormone deficiency that is ONE of the following (i or ii): **[documentation required for all elements]**

iii. Childhood onset; OR

iv. Adult onset that results from one of the following: growth hormone deficiency alone or multiple hormone deficiencies (hypopituitarism) resulting from pituitary disease, hypothalamic disease, pituitary surgery, cranial radiation therapy, tumor treatment, traumatic brain injury, or subarachnoid hemorrhage; AND

C) Patient meets at least ONE of the following (i, ii, or iii):

iv. Patient (adult or transition adolescent) has known perinatal insults OR congenital or genetic defects; **[documentation required]** OR

v. Patient meets ALL of the following (a, b, and c):

d) Patient (adult onset or transition adolescent) has three or more of the following pituitary hormone deficiencies: Adrenocorticotropic hormone , thyroid-stimulation hormone, gonadotropin deficiency (luteinizing hormone and/or follicle stimulating hormone deficiency are counted as one deficiency), and prolactin **[documentation required]**; AND

e) The age and gender adjusted serum insulin-like growth factor-1 is below the lower limit of the normal reference range for the reporting laboratory **[documentation required]**; AND

f) Other causes of low serum insulin-like growth factor-1 have been excluded (e.g., malnutrition, prolonged fasting, poorly controlled diabetes mellitus, hypothyroidism, hepatic insufficiency, oral estrogen therapy); OR

vi. Patient meets at least ONE of the following (a or b):

a) Adult. Patient has had a negative response to at least ONE of the following standard growth hormone stimulation tests (1, 2, 3, 4, 5, or 6) **[documentation required for all elements]**:

Note: If the patient has had a previous trial of an arginine test with a peak response of ≤ 0.4 mcg/L, this would meet the criteria for a negative response to a growth hormone stimulation test.

(1) Insulin tolerance test (obtaining at least 3 growth hormone levels in at least a 60 minute timeframe [not including a level at timeframe zero], with adequate hypoglycemia being achieved) with peak response ≤ 5.0 mcg/L; OR

(2) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with peak response ≤ 3.0 mcg/L AND the patient's body mass index (BMI) is < 25 kg/m^2; OR

(3) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with a peak response ≤ 3.0 mcg/L AND the patient's BMI is ≥ 25 kg/m^2 and ≤ 30 kg/m^2 with, according to the prescriber, a high pretest probability of growth hormone deficiency; OR

(4) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with a peak response ≤ 1.0 mcg/L AND the patient's BMI is ≥ 25 kg/m^2 and ≤ 30 kg/m^2 with, according to the prescriber, a low pretest probability of growth hormone deficiency; OR

(5) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with peak response ≤ 1.0 mcg/L AND the patient's BMI is > 30 kg/m^2; OR

(6) Macrilen (macimorelin oral solution) test (obtaining at least 4 growth hormone levels in at least a 90 minute timeframe [not including a level at timeframe zero]) with peak responses < 2.8 ng/mL (2.8 mcg/L) AND the patient's BMI is ≤ 40 kg/m^2.
Note: The following formula can be used to calculate BMI: BMI equals body weight in kg divided by height meters squared (m^2) [i.e., BMI = kg/m^2]; OR

b) Transition adolescent. Patient meets BOTH of the following (1 and 2): **[documentation required for all elements]**:

Note: The transition period is the time from late puberty to establishment of adult muscle and bone composition, and encompasses attainment of adult height.

Note: If the patient has had a trial of a Macrilen test with a peak response of < 2.8 ng/mL (mcg/L), this would meet the criteria for a negative response to a growth hormone stimulation test.

(3) Patient has been off growth hormone therapy for at least 1 month before retesting with a growth hormone stimulation test; AND

(4) Patient meets at least ONE of the following responses to growth hormone stimulation testing (i, ii, iii, iv, v or vi):

(vii) Insulin tolerance test (obtaining at least 3 growth hormone levels in at least a 60 minute timeframe [not including a level at timeframe zero], with adequate hypoglycemia being achieved) with peak response ≤ 5.0 mcg/L; OR

(viii) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with peak response ≤ 3.0 mcg/L AND the patient's body mass index (BMI) is < 25 kg/m^2; OR

(ix) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with a peak response of ≤ 3.0 mcg/L AND the patient's BMI is ≥ 25 kg/m^2 and ≤ 30 kg/m^2 with, according to the prescriber, a high pretest probability of growth hormone deficiency; OR

(x) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with a peak

response ≤ 1.0 mcg/L AND the patient's BMI is ≥ 25 kg/m^2 and ≤ 30 kg/m^2 with, according to the prescriber, a low pretest probability of growth hormone deficiency; OR

(xi) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with peak response ≤ 1.0 mcg/L AND the patient's BMI is > 30 kg/m^2; OR

(xii) If both the insulin tolerance test AND glucagon stimulation test are contraindicated, the arginine test can be used (obtaining at least 3 growth hormone levels in at least 120 minute timeframe [not including a level at timeframe zero]) with a peak response ≤ 0.4 mcg/L; AND

D) Patient has been evaluated by an endocrinologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sogroya is not recommended in the following situations:
Note: For some of the following indications, authorization for coverage is not recommended because this indication is excluded from coverage in a typical pharmacy benefit.

1. **Acute Critical Illness Due to Complications Following Surgery, Multiple Accidental Trauma, or with Acute Respiratory Failure.**[1] Sogroya is contraindicated in acute critical illness after open-heart surgery, abdominal surgery, multiple accidental trauma, or those with acute respiratory failure because of the risk of increased mortality.

2. **Aging (i.e., Anti-Aging), to Improve Functional Status in an Elderly Patient, and Somatopause.**[13,14,17,18] Somatropin is not FDA-approved for anti-aging therapy, to improve functional status in elderly patients, or to treat somatopause. Federal law prohibits the distribution or dispensing of somatropin for non-FDA approved uses. There are no long-term studies assessing somatropin efficacy and safety for anti-aging therapy. Short-term therapy with somatropin may improve some measures of body composition, including increased muscle mass, reduced total body fat, improved skin elasticity, and reduced rate of bone demineralization, but somatotropin does not have positive effects on strength, functional capacity, or metabolism. Somatropin is associated with considerable adverse effects in non-growth hormone deficient adults (e.g., carpal tunnel syndrome, soft tissue edema, arthralgias, glucose intolerance, increased serum lipids). Another concern is the possible increased risk of cancer with long-term use of somatropin and the potentiating effects of IGFs on cancer. Somatropin is not indicated for the age-related decrease in growth hormone/IGF-1 status.[12]

3. **Athletic Ability Enhancement.**[5] Somatropin is not FDA-approved for athletic performance enhancement or for body building in nonathletes. Federal law prohibits the distribution or dispensing of somatropin for non-FDA approved uses. Short-term administration of somatropin to increase strength and endurance in athletes is no more effective than training alone and somatropin should not be administered to athletes or other persons for the purpose of enhancing athletic ability or improving personal appearance (i.e., to appear leaner and more muscular). Somatropin has been used in supraphysiologic doses alone or in combination with other performance enhancing drugs (PEDs) in users who are not athletes.[3,4] Use of PEDs has been linked to an increased risk of death and many adverse effects including cardiovascular, psychiatric, metabolic, endocrine, neurologic, infectious, hepatic, renal, and musculoskeletal disorders.

4. **Central Precocious Puberty.** Children with precocious puberty are often treated with gonadotropin releasing hormone (GnRH) agonists (Lupron® [leuprolide acetate injection]) to suppress pituitary gonadal activity, to slow the advancement of bone age (prevent premature fusion of the epiphyseal

growth plates), and to improve adult height. In some patients GnRH agonist therapy may result in marked deceleration of bone growth and may result in adult height that is less than the mid-parental height. Somatropin has been used in girls when growth velocity decreases or if it appears that the targeted adult height will not be attained.[6] There are no large well-controlled trials on the efficacy and safety of adding somatropin to GnRH agonist therapy in these children or the effect on final height.[6,7]

5. **Chronic Fatigue Syndrome.** There is no evidence of GHD in chronic fatigue syndrome.[19]

6. **Congenital Adrenal Hyperplasia (CAH).**[8,9] The Endocrine Society clinical practice guidelines on CAH due to steroid 21-hydroxylase deficiency recommend against the use of experimental treatment approaches outside of formally approved clinical trials.[9] Children with predicted adult height standard deviation $\leq$ -2.25 may be considered for growth-promoting treatments in appropriately controlled trials.

7. **Constitutional Delay of Growth and Puberty.** These children have delayed skeletal maturation and pubertal development. Administering somatropin does not increase adult height (which is usually normal).[10] Short-term androgen therapy accelerates growth and the rate of pubertal advancement in boys.

8. **Fibromyalgia.** In one placebo-controlled study, 120 non-GHD adult women with severe fibromyalgia and low levels of IGF-1 were randomized to somatropin 0.006 mg/kg/day for 12 months (dose was adjusted) or placebo for 6 months.[20] Patients receiving placebo initially were switched to somatropin from Months 6 to 12 (open label). Standard therapy for fibromyalgia was continued. After 6 months, there were no differences between somatropin and placebo in the percentage of patients with fewer than 11 positive tender points, mean number of tender points, intensity of pain in every point evaluated, and other measures. After 12 months of somatropin therapy, 53% of patients had less than 11 positive tender points compared with 33% of patients who received placebo and then somatropin for 6 months ($P < 0.05$). At 18 months follow-up evaluation when somatropin was discontinued, impairment in pain perception worsened in both groups but to a lesser extent in the patients on somatropin for 12 months. Further controlled trials are needed with a longer duration,[21] with different doses, and using the 2010 American College of Rheumatology criteria for fibromyalgia. Some patients with fibromyalgia may have adult GHD.

9. **Infertility.**[22,23] Clinical trials indicate that somatropin is not useful as an adjunct during in vitro fertilization, for induction of ovulation in polycystic ovary syndrome, or for assisted reproductive technology. The authors of a recent meta-analysis concluded there is no evidence of an increased chance of a live birth with use of somatropin.

10. **Obesity.**[24,25] Somatropin is not indicated for the treatment of obesity. Low growth hormone levels are a consequence of central obesity and not a cause. Obesity is associated with decreased basal and pulsatile release of growth hormone and decreased stimulated growth hormone release. Somatropin therapy does not have significant beneficial effects on obesity in persons without GHD and does not produce significant overall weight loss. Supraphysiologic doses of somatropin have been used to treat obesity. Effects of long-term therapy with somatropin are unknown.

11. **Osteoporosis.**[26,27] Guidelines for treatment or prevention of osteoporosis do not include recommendations for use of somatropin. In one double-blind trial, 80 postmenopausal women with osteoporosis (56% of patients [n = 45/80] had a of fractures) were randomized to somatropin 0.33 mg/day or 0.83 mg/day or to placebo for three years.[26] The double-blind phase was 18 months and patients on somatropin continued drug for another 18 months and patients on placebo stopped at 18 months. Patients were compared with an age-matched random population sample of women (n = 120).

All patients received calcium 750 mg, vitamin D 400 units, and hormone replacement therapy. All women were followed for 10 years total. Bone mineral density increased in the patients receiving somatropin at years 4 and 5, and after 10 years, had decreased to similar levels as before treatment. At 10 years, 28% of women (n = 22/80) had had fractures. In the control group, fractures increased from 8% of patients at baseline to 32% of patients after 10 years. At 10 years, 41% of patients (n = 33/80) had stopped hormone replacement therapy; 23% had started bisphosphonates due to fractures, and 3% had received Forteo® (teriparatide injection). Larger studies are needed to determine the effects of somatropin therapy on bone mineral density and fractures in non-growth hormone deficient persons.

12. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Growth Disorders – Voxzogo Prior Authorization Policy
- Voxzogo™ (vosoritide subcutaneous injection – BioMarin)

REVIEW DATE: 11/01/2023

OVERVIEW

Voxzogo, a C type natriuretic peptide (CNP) analog, is indicated **to increase linear growth in pediatric patients with achondroplasia** with open epiphyses.[1]

Disease Overview

Achondroplasia is the most common form of disproportionate short stature in humans.[2] It is a primary skeletal dysplasia caused by a mutation in the fibroblast growth factor receptor 3 (FGFR3) gene; this mutation leads to impaired endochondral ossification. Achondroplasia occurs in approximately 1 in 20,000 to 30,000 live births.[3] It occurs as a result of a spontaneous mutation in 80% of patients (i.e., both parents are of normal height).[4] In the remaining 20% of patients, the mutation is inherited from a parent. Achondroplasia is characterized by short stature, long-bone shortening in the proximal upper and lower extremities, and macrocephaly. The diagnosis can be confirmed by molecular testing.[5] In the pivotal trial for Voxzogo, achondroplasia was confirmed by genetic testing in all patients.[2] Additionally, exclusion criteria included the evidence of decreased growth velocity (< 1.5 cm/year) or of growth plate closure through bilateral lower extremity X-rays.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Voxzogo. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Voxzogo as well as the monitoring required for adverse events and long-term efficacy, approval requires Voxzogo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Voxzogo is recommended in those who meet the following criteria:

FDA-Approved Indication

41. Achondroplasia. Approve for 1 year if the patient meets ONE of the following (A or B):
- **A)** Initial Therapy or Patient Has Been on Voxzogo < 1 Year. Approve if the patient meets ALL of the following (i, ii, iii, iv, v, and vi):
  - **i.** Patient is < 18 years of age; AND
  - **ii.** The diagnosis of achondroplasia has been confirmed by genetic testing with an identifiable mutation in the fibroblast growth factor receptor type 3 (FGFR3) gene; AND
  - **iii.** Patient's epiphyses are open; AND
  - **iv.** Patient will not have limb-lengthening surgery during treatment with Voxzogo; AND

v. The prescriber has confirmed the patient is able to drink approximately 240 to 300 mL of fluid in the hour prior to Voxzogo administration; AND
vi. The medication is prescribed by or in consultation with a pediatric endocrinologist.

B) Patient Has Been Receiving Voxzogo for ≥ 1 Year. Approve if the patient meets ALL of the following (i, ii, iii, iv, v, vi, and vii):
i. Patient is < 18 years of age; AND
ii. The diagnosis of achondroplasia has been confirmed by genetic testing with an identifiable mutation in the fibroblast growth factor receptor type 3 (FGFR3) gene; AND
iii. Patient's epiphyses are open; AND
iv. Patient will not have limb-lengthening surgery during treatment with Voxzogo; AND
v. The prescriber has confirmed the patient is able to drink approximately 240 to 300 mL of fluid in the hour prior to Voxzogo administration; AND
vi. The medication is prescribed by or in consultation with a pediatric endocrinologist; AND
vii. Patient's most recent annualized growth velocity continues to be above their baseline annualized growth velocity value (i.e., before the patient started on Voxzogo).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Voxzogo is not recommended in the following situations:

90. Hypochondroplasia, Thanatophoric Dysplasia, or other Short Stature Conditions other than Achondroplasia (e.g., trisomy 21, pseudoachondroplasia). Voxzogo is only indicated for patients with achondroplasia.[1] There is no evidence Voxzogo is effective for other short stature conditions.

91. Concurrent Treatment with Growth Hormone (e.g., somatropin), Long-Acting Growth Hormone (e.g., Ngenla® {somatrogon-ghla}, Skytrofa® {lonapegsomatropin}, Sogroya® {somapacitan-beco}), or Insulin-like Growth Factor- 1 (IGF-1) [i.e., Increlex® {mecasermin}] Agents. Growth hormone agents and Increlex are NOT indicated to increase growth in patients with achondroplasia.[6-10] Additionally, there are no available studies demonstrating the safety or efficacy of concurrent use with Voxzogo.

92. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Adzynma Prior Authorization Policy
- Adzynma™ (ADAMTS13 recombinant-krhn intravenous infusion – Takeda)

REVIEW DATE: 12/06/2023

OVERVIEW

Adzynma, a human recombinant "A disintegrin and metalloproteinase with thrombospondin motifs 13" (ADAMTS13) product, is indicated for prophylactic or on demand enzyme replacement therapy for the management of congenital thrombotic thrombocytopenia purpura in adult and pediatric patients.[1]

Disease Overview

Congenital thrombotic thrombocytopenic purpura is a very rare, inherited blood clotting disorder.[2,3] It is due to a mutation in the ADAMTS13 gene that makes a key enzyme, also named ADAMTS13, that regulates blood clotting. A deficiency in this enzyme causes blood clots to form in the small blood vessels throughout the body. The disease impacts fewer than 1,000 people in the US. Symptoms typically start in infancy or early childhood, but in some cases may develop in adulthood and can initially manifest during pregnancy. Patients with congenital thrombotic thrombocytopenic purpura may experience severe bleeding episodes, strokes, and damage to vital organs. The condition can be fatal if not managed. Treatment for congenital thrombotic thrombocytopenic purpura currently involves prophylactic plasma-based therapy to reduce the risk of clotting/bleeding by replenishing the absent/low ADAMTS13 enzyme; on-demand therapy can also be given.

Guidelines

Adzynma has not been specifically addressed in guidelines post FDA-approval.[4] The International Society on Thrombosis and Haemostasis (ISTH) has guidelines for the treatment of thrombotic thrombocytopenic purpura (2020). For patients with congenital thrombotic thrombocytopenic purpura who are in remission, the panel suggests either plasma infusion or a watch and wait strategy. For patients with congenital thrombotic thrombocytopenic purpura who are pregnant, the panel recommends prophylactic treatment over no prophylactic treatment. In this clinical scenario, plasma infusion is recommended over Factor VIII products.

The British Society of Haemtology published guidelines for the diagnosis and management of thrombotic thrombocytopenic purpura and thrombotic microangiopathies.[5] The diagnosis of congenital thrombotic thrombocytopenic purpura is defined by ADAMTS13 activity < 10 IU/dL, no anti-ADAMTS13 antibodies, and confirmation of homozygous or compound heterozygous variants in the ADAMTS13 gene. For an acute episode, solvent detergent plasma infusion is recommended. ADAMTS13 prophylaxis should be considered for all patients with an individualized approach to dose and frequency according to symptoms, whether overt or non-overt. For pregnant women with congenital thrombotic thrombocytopenic purpura, regular solvent/detergent fresh frozen plasma replacement therapy should be given prophylactically to prevent clinical relapse.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Adzynma. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Adzynma as well as the monitoring required for adverse events and long-term efficacy, approval requires Adzynma to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Adzynma as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory data, genetic test results, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Adzynma is recommended in those who meet the following criteria:

FDA-Approved Indication

42. Congenital Thrombotic Thrombocytopenic Purpura. Approve for 1 year if the patient meets the following (A, B, C, and D):

A) At baseline (prior to therapy) ADAMTS13 activity is < 10% (< 10 IU/dL) **[documentation required]**; AND

Note: Baseline refers to before any treatment was received, such as Adzynma or plasma-based therapies.

B) Patient does not have anti-ADAMTS13 autoantibodies as determined by a diagnostic test **[documentation required]**; AND

C) Patient has a pathogenic variant or a mutation in the ADAMTS13 gene **[documentation required]**; AND

Note: Pathogenic variants or gene mutations are usually homozygous or compound heterozygous.

D) Medication is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Adzynma is not recommended in the following situations:

93. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Aphexda Utilization Management Medical Policy
- Aphexda™ (motixafortide subcutaneous injection – BioLineRx)

REVIEW DATE: 11/15/2023

OVERVIEW

Aphexda, a hematopoietic stem cell mobilizer, is indicated in combination with filgrastim (granulocyte colony stimulating factor) to **mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with multiple myeloma**.[1]

Disease Overview

Multiple myeloma is a cancer formed by malignant plasma cells found in the bone marrow.[2,3] In 2023, it is estimated that there will be approximately 35,730 new cases of multiple myeloma and 12,590 deaths due to the disease. There are many therapies available for multiple myeloma. Autologous stem cell transplantation (ASCT) has a vital role in the treatment of multiple myeloma. The outcomes of ASCT relies on the collection of sufficient hematopoietic stem and progenitor cells, usually from peripheral blood.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Aphexda. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Aphexda as well as the monitoring required for adverse events and long-term efficacy, approval requires Aphexda to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Aphexda is recommended in those who meet the following criteria:

FDA-Approved Indication

43. Multiple Myeloma. Approve for 1 month if the patient meets the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The agent is utilized for mobilization of hematopoietic stem cells for subsequent autologous transplantation; AND
- **C)** Use is in combination with filgrastim; AND
  Note: Examples of filgrastim products include Granix (tbo-filgrastim subcutaneous injection) and Neupogen (filgrastim subcutaneous injection and intravenous infusion), as well as related biosimilars.
- **D)** Medication is prescribed by a hematologist and/or a stem cell transplant specialist physician.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Aphexda is not recommended in the following situations:

94. Leukemia. Aphexda may cause mobilization of leukemia cells and subsequent contamination of the apheresis product.[1] Aphexda is not intended for hematopoietic stem cell mobilization and harvest in patients with leukemia.

95. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Cablivi Prior Authorization Policy
- Cablivi® (caplacizumab-yhdp intravenous infusion or subcutaneous injection – Genzyme)

REVIEW DATE: 02/22/2023

Overview

Cablivi, a von Willebrand factor (vWF)-directed antibody fragment, is indicated for the treatment of **acquired thrombotic thrombocytopenic purpura** (aTTP) in adults, in combination with plasma exchange and immunosuppressive therapy.[1] Two doses of Cablivi are given on the first day of plasma exchange, followed by one dose of Cablivi per day during plasma exchange; treatment is continued for 30 days after the last plasma exchange session. If, after the initial treatment course, there are signs of persistent underlying disease such as suppressed ADAMTS13 (A Disintegrin And Metalloproteinase with ThromboSpondin-1 motif, member 13) levels, Cablivi therapy may be extended for a maximum of 28 days. Cablivi should be discontinued if the patient experiences more than two recurrences of aTTP while on Cablivi. Cablivi increases the risk of bleeding; the risk of bleeding is further increased in patients with underlying coagulopathies (e.g., hemophilia, other coagulation factor deficiencies) and in patients receiving Cablivi concomitantly with drugs that affect hemostasis and coagulation.

Disease Overview

Thrombotic thrombocytopenic purpura (TTP) is a rare but potentially fatal blood disorder.[2-5] TTP may be caused by an inherited severe deficiency of plasma ADAMTS13 activity resulting from mutations; this is referred to as hereditary or congenital TTP. More commonly, TTP is acquired and due to autoantibodies that inhibit plasma ADAMTS13 activity, referred to as immune-mediated TTP (iTTP). Reduced ADAMTS13 activity leads to accumulation of ultra-large vWF multimers in the blood, which bind to platelets and lead to excessive platelet clumping in the microvasculature, resulting in multi-organ failure and death. Cablivi is a nanobody that targets the ultra-large vWF and inhibits the interaction between vWF and platelets, thereby preventing platelet adhesion.[1-3,6]

Guidelines/Recommendations

The standard of care for treatment of aTTP is plasma exchange and glucocorticoids.[7] Plasma exchange removes the ultra-large vWF and autoantibodies and replenishes ADAMTS13, and immunosuppressants inhibit autoantibody formation.[2,6,7] Rituximab can also be added to the aTTP treatment regimen.[3] Rituximab has been shown to reduce the incidence of aTTP relapse by diminishing the production of anti-ADAMTS13 antibodies and restoring ADAMTS13 activity.[3,4]

The International Society on Thrombosis and Haemostasis (ISTH) formed a multidisciplinary panel including hematologists and pathologists with clinical expertise in the diagnosis and management of TTP, clinicians from other relevant disciplines, and patient representatives to issue recommendations about treatment of TTP (2020).[8] For patients with aTTP or iTTP experiencing an acute event (first event or relapse), the panel suggests using Cablivi over not using Cablivi. The panel stressed that Cablivi should only be given under the guidance of an experienced clinician, ideally a TTP expert (e.g., a hematologist or pathologist specialized in transfusion medicine with previous experience in treating the disease).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cablivi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cablivi as well as the monitoring required for adverse events and efficacy, approval requires Cablivi to be prescribed by or in consultation with a physician who specializes in the condition being treated. Note that one course of treatment consists of Cablivi to be administered in conjunction with plasma exchange and Cablivi to be administered for up to 60 days (one dose per day) following the last plasma exchange session.

Automation: None.

Recommended Authorization Criteria

Coverage of Cablivi is recommended in those who meet the following criteria:

FDA-Approved Indication

19. Acquired Thrombotic Thrombocytopenic Purpura. Approve for one course of treatment (up to 60 days following the last plasma exchange session) if the patient meets ALL of the following criteria (A, B, C, D, and E):

K) Patient is ≥ 18 years of age; AND

L) Cablivi was initiated in the inpatient setting, in combination with plasma exchange therapy; AND

M) Patient is currently receiving at least one immunosuppressive therapy; AND

EE) Note: Examples include systemic corticosteroids, rituximab (or a rituximab product), cyclosporine, cyclophosphamide, mycophenolate mofetil, hydroxychloroquine, bortezomib.

N) If the patient has previously received Cablivi, he/she has not had more than two recurrences of acquired thrombotic thrombocytopenic purpura while on Cablivi; AND

O) The medication is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cablivi is not recommended in the following situations:

24. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Cablivi® for injection [prescribing information]. Cambridge, MA: Genzyme; February 2022.
2. Duggan S. Caplacizumab: first global approval. *Drugs*. 2018;78:1639-1642.
3. Coppo P, Cuker A, George JN. Thrombotic thrombocytopenic purpura: toward targeted therapy and precision medicine. *Res Pract Thromb Haemost*. 2019;3:26-37.
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5. Zheng XL, Vesely SK, Cataland SR, et al. International Society on Thrombosis and Haemostasis (ISTH) guidelines for the diagnosis of thrombotic thrombocytopenic purpura. *J Thromb Haemost*. 2020;18:2486-2495.
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8. Zheng XL, Vesely SK, Cataland SR, et al. International Society on Thrombosis and Haemostasis (ISTH) guidelines for the treatment of thrombotic thrombocytopenic purpura. *J Thromb Haemost*. 2020;18:2496-2502.

PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Ceprotin Prior Authorization Policy
- Ceprotin® (protein C concentrate [human] intravenous infusion – Baxalta/Shire)

REVIEW DATE: 11/08/2023

OVERVIEW

Ceprotin is indicated for pediatric and adult patients with **severe congenital protein C deficiency** for the prevention and treatment of venous thrombosis and purpura fulminans.[1]

Disease Overview

Mutations in the *PROC* gene lead to deficiency of protein C, which is a natural anticoagulant.[2] Individuals with heterozygous *PROC* mutation present with milder disease but are at risk for development of venous thromboembolism. Those who have mutations in both *PROC* genes develop severe symptoms within a few hours to days after birth. In severe protein C deficiency, a complication called purpura fulminans may arise in which blood clots form throughout the body. Blood clots affect the extremities most often but can become widespread (disseminated intravascular coagulation), leading to tissue necrosis.

Diagnosis is based on characteristic symptoms and detailed family history, in addition to measurement of protein C activity or antigen levels.[3,4] It is critical to exclude any acquired reason for protein C deficiency, which is more common than congenital protein C deficiency.[3] Potential causes of acquired deficiency include vitamin K antagonists (e.g., warfarin), vitamin K deficiency, chronic liver disease, recent thrombosis, recent surgery, or disseminated intravascular coagulation. Diagnostic recommendations from the International Society of Thrombosis and Hemostasis recommend waiting until 30 days after vitamin K antagonist treatment ends to perform protein C assay testing.[4] Molecular genetic testing is only available in a few research laboratories and is not routinely used in clinical diagnosis.[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ceprotin. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ceprotin as well as the monitoring required for adverse events and long-term efficacy, approval requires Ceprotin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ceprotin is recommended in those who meet the following criteria:

FDA-Approved Indication

37. Protein C Deficiency, Severe. Approve for 1 year if the patient meets the following (A, B, C, and D)
- The diagnosis of protein C deficiency is confirmed by at least one of the following (i, ii, or iii):

- Plasma protein C activity below the lower limit of normal based on the age-specific reference range for the reporting laboratory; OR
- Plasma protein C antigen below the lower limit of normal based on the age-specific reference range for the reporting laboratory; OR
- Genetic testing demonstrating biallelic mutations in the *PROC* gene; AND

- Acquired causes of protein C deficiency have been excluded; AND

Note: Examples of acquired causes of protein C deficiency include recent use of vitamin K antagonists (e.g., warfarin) within 30 days, vitamin K deficiency, chronic liver disease, recent thrombosis, recent surgery, or disseminated intravascular coagulation.

- According to the prescriber, patient has a current or prior of symptoms associated with severe protein C deficiency (e.g., purpura fulminans, thromboembolism); AND
- Ceprotin is being prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ceprotin is not recommended in the following situations:

96. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

362. Ceprotin® intravenous infusion [prescribing information]. Lexington, MA: Baxalta/Shire; August 2021.

363. Protein C Deficiency. National Organization of Rare Disorders. Updated 2016. Available at: https://rarediseases.org/rare-diseases/protein-c-deficiency/. Accessed on November 8, 2023.

364. Dinarvand P, Moser KA. Protein C deficiency. *Arch Pathol Lab Med*. 2019;143(10):1281-1285.

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PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Coagadex Prior Authorization Policy
- Coagadex® (coagulation Factor X [human] intravenous infusion – BPL)

REVIEW DATE: 11/08/2023

OVERVIEW

Coagadex, a plasma-derived coagulation Factor X product, is indicated for use in adults and children with hereditary Factor X deficiency for:[1-3]

- **On-demand treatment and control** of bleeding episodes.
- **Perioperative management** of bleeding in patients with mild and moderate hereditary Factor X deficiency.
- **Routine prophylaxis** to reduce the frequency of bleeding episodes.

Disease Overview

Factor X deficiency, a rare autosomal recessive inherited bleeding disorder, affects approximately 1 in 500,000 to 1,000,000 patients worldwide.[4,5] The Factor X protein has a key role to assist in activating the enzymes that are key in clot formation. In this condition, blood does not clot properly. Patients experience easy bruising, nose or mouth bleeds, and bleeding after trauma or surgery. Among patients with severe Factor X deficiency, umbilical cord bleeding can be one of the first signs; however, bleeding may present at any time. Serious bleeds include spontaneous head bleeds, spinal cord bleeds, and gastrointestinal bleeds. Women who have the condition may experience heavy menstrual bleeding or have menorrhagia. During pregnancy, women may miscarry during the first trimester or have other complications during labor and delivery. However, Factor X deficiency has an equal prevalence in men and women. It is recommended to maintain trough levels of around 20% to 30%. Other treatments include fresh frozen plasma, prothrombin complex concentrates, and Coagadex.

Guidelines

The National Bleeding Disorders Foundation Medical and Scientific Advisory Council has guidelines for the treatment of hemophilia and other bleeding disorders (revised August 2023).[6] Coagadex is recommended in patients who have Factor X deficiency.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Coagadex. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Coagadex as well as the monitoring required for adverse events and long-term efficacy, approval requires Coagadex to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Coagadex is recommended in those who meet the following criteria:

FDA-Approved Indication

44. Hereditary Factor X Deficiency. Approve for 1 year if the agent is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Coagadex is not recommended in the following situations:

97. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

366. Coagadex® intravenous infusion [prescribing information]. Durham, NC: BPL; April 2023.
367. Escobar MA, Kavakli K. Plasma-derived human factor X concentrate for the treatment of patients with hereditary factor X deficiency. *Hemophilia*. 2023 Oct 30. [Online ahead of print].
368. Payne J, Batsuli G, Leavitt AD, et al. A review of the pharmacokinetics, efficacy, safety of high-purity factor X for the prophylactic treatment of hereditary factor X deficiency. *Haemophilia*. 2022;28(4):523-531.
369. Menegatti M, Peyvandi F. Treatment of rare factor deficiencies other than hemophilia. *Blood*. 2019;133(5):415-424.
370. Peyvandi F, Auerswald G, Austin SK, et al. Diagnosis, therapeutic advances, and key recommendations for the management of factor X deficiency. *Blood Rev*. 2021 Nov;50:100833.
371. National Bleeding Disorders Foundation. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and selected disorders of the coagulation system (August 2023). MASAC Document #280. Available at: https://www.hemophilia.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed on November 5, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Corifact Prior Authorization Policy
- Corifact® (Factor XIII Concentrate [human] intravenous infusion – CSL Behring)

REVIEW DATE: 11/08/2023

OVERVIEW

Corifact, a Factor XIII concentrate, is indicated for adult and pediatric patients with congenital Factor XIII deficiency for:[1]

- **Peri-operative management** of surgical bleeding.
- **Routine prophylactic** treatment.

Disease Overview

Congenital Factor XIII deficiency is caused by defects in both Factor XIIIA and Factor XIIIB genes.[2,3] However, most cases are due to genetic alterations on the Factor XIIIA gene. The estimated prevalence of Factor XIIIA deficiency is one case in 2 million patients. Clinical symptoms include delayed wound healing, bleeding of soft and subcutaneous tissue, recurrent spontaneous miscarriage, and central nervous system (CNS) bleeding, which may be life-threatening. If patients have severe Factor XIII deficiency, early manifestations include bleeding from the umbilical cord or CNS. Prospective data showed that a level of 30% Factor XIII clotting activity is an adequate therapeutic target for most patients. Treatment of Factor XIII deficiency involves use of fresh frozen plasma, cryoprecipitate, Corifact, or Tretten® (coagulation Factor XIIIA-Subunit [recombinant] intravenous infusion).

Guidelines

The National Bleeding Disorders Foundation Medical and Scientific Advisory Council has guidelines for the treatment of hemophilia and other bleeding disorders (revised August 2023).[4] Corifact is recommended in patients who have Factor XIII deficiency.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Corifact. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Corifact as well as the monitoring required for adverse events and long-term efficacy, approval requires Corifact to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Corifact is recommended in those who meet the following criteria:

FDA-Approved Indication

45. Congenital Factor XIII Deficiency. Approve for 1 year if the agent is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Corifact is not recommended in the following situations:

98. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

372. Corifact® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; September 2020.
373. Menegatti M, Peyvandi F. Treatment of rare factor deficiencies other than hemophilia. *Blood*. 2019;133(5):415-424.
374. Pelcovits A, Schiffman F, Niroula R. Factor XIII deficiency: a review of clinical presentation and management. *Hematol Oncol Clin North Am*. 2021;35(6):1171-1180.
375. National Bleeding Disorders Foundation. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and selected disorders of the coagulation system (August 2023). MASAC Document #280. Available at: https://www.hemophilia.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed on November 5, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Enjaymo Prior Authorization Policy
- Enjaymo® (sutimlimab-jome intravenous infusion – Bioverativ/Sanofi)

REVIEW DATE: 01/03/2024

OVERVIEW

Enjaymo, a classical complement inhibitor, is indicated for the treatment of hemolysis in **cold agglutinin disease** in adults.[1]

Disease Overview

Cold agglutinin disease is a rare autoimmune hemolytic anemia.[2-4] Primary cold agglutinin disease is a B-cell lymphoproliferative disorder in which autoantibodies are produced against erythrocyte surface antigens. Primary cold agglutinin disease is distinct from secondary disease, termed cold agglutinin syndrome, which can occur with underlying conditions such as malignancy, infection, and autoimmune diseases.[2,3] Diagnosis of cold agglutinin disease is defined by chronic hemolysis, a cold agglutinin titer ≥ 64 at 4°C, and typical findings on direct antibody test (DAT), which include strong positivity for complement protein C3d and negativity (or only weak positivity) for immunoglobulin G.[2-4] Secondary causes of cold agglutinin syndrome should be excluded. Importantly, patients without chronic hemolysis or circulatory symptoms do not have cold agglutinin disease, even in the presence of positive DAT.[2] Symptoms include cold-induced circulatory symptoms, which can range from slight acrocyanosis to severe Raynaud phenomena. Anemia is generally considered mild to moderate with a median hemoglobin (Hb) of 8.9 g/dL; however, the lower tertile Hb was 8.0 g/dL and ranged to as low as 4.5 g/dL.[2,4]

Clinical Efficacy

In the pivotal CARDINAL trial (published) [n = 24], patients were required to have a confirmed diagnosis of cold agglutinin disease based on chronic hemolysis, typical DAT findings, and a recent blood transfusion within the prior 6 months.[1,5-7] Patients were also required to have a baseline hemoglobin level < 10 g/dL and total bilirubin above normal. Approximately two-thirds of patients had failed other therapies (e.g., rituximab). The Phase III CADENZA trial (published) [n = 42] also required chronic hemolysis, as well as the DAT and cold agglutinin titer findings described above; however, recent history of blood transfusion was not required.[1,8]

Guidelines

An international consensus guideline for autoimmune hemolytic anemias was published in 2020.[9] The guideline was published prior to the approval of Enjaymo and no formal recommendation is made regarding its place in therapy, although positive Phase I data are acknowledged. It is noted that clinical and histological assessment, as well as radiologic examinations as needed, are necessary to rule out cold agglutinin syndrome secondary to malignant disease. Treatment of cold agglutinin syndrome involves supportive care and management of the underlying disease. For treatment of cold agglutinin disease, asymptomatic patients should be managed with watchful waiting. For symptomatic patients (i.e., those with anemia, transfusion, or circulatory symptoms), rituximab is the best-documented first-line treatment and may be given alone or in combination with bendamustine. For second-line treatment, the combination of rituximab plus bendamustine is recommended (if not given in the first-line setting). Alternatively, rituximab monotherapy may be repeated for patients who previously responded for at least 1 year. Rituximab plus fludarabine is an option for fit, elderly patients. There are no evidence-based therapies for the third-line setting.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Enjaymo. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Enjaymo as well as the monitoring required for adverse events and long-term efficacy, approval requires Enjaymo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Enjaymo is recommended in those who meet the following criteria:

FDA-Approved Indication

46. Cold Agglutinin Disease. Approve for 1 year if the patient meets the following (A, B, C, D, E, F, G, and H):

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient weighs ≥ 39 kg; AND
- **C)** Patient has a of at least one sign or symptom associated with cold agglutinin disease; AND
  Note: Examples include symptomatic anemia (e.g., anemia associated with fatigue, weakness, shortness of breath, heart palpitations, lightheadedness, chest pain), acrocyanosis, Raynaud's syndrome, hemoglobinuria, disabling circulatory symptoms, or a major adverse vascular event (e.g., thrombosis).
- **D)** According to the prescriber, the patient has evidence of chronic hemolysis; AND
- **E)** Patient meets the following diagnostic criteria (i and ii):
  - **i.** Direct antibody test strongly positive for C3d and negative or only weakly positive for immunoglobulin G; AND
  - **ii.** Cold agglutinin antibody titer ≥ 64 at 4°C (approximately 40°F); AND
- **F)** At baseline (prior to the initiation of Enjaymo), patient meets both of the following (i and ii):
  - **i.** Hemoglobin ≤ 10 g/dL; AND
  - **ii.** Total bilirubin above the upper limit of normal, based on the reference range for the reporting laboratory; AND
- **G)** According to the prescriber, secondary causes of cold agglutinin syndrome have been excluded; AND
  Note: Examples of secondary causes of cold agglutinin syndrome include infection, rheumatologic diseases, and active hematologic malignancies.
- **H)** Enjaymo is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Enjaymo is not recommended in the following situations:

99. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

376. Enjaymo® intravenous infusion [prescribing information]. Waltham, MA: Bioverativ/Sanofi; March 2023.

377. Berentsen S, Röth A, Randen U, et al. Cold agglutinin disease: current challenges and future prospects. *J Blood Med*. 2019;10:93-103.
378. Berentsen S. How I treat cold agglutinin disease. *Blood*. 2021;137(10):1295-1303.
379. Swiecicki PL, Hegerova LT, Gertz MA. Cold agglutinin disease. *Blood*. 2013;122(7):1114-1121.
380. Röth A, Barcellini W, D'Sa S, et al. Sutimlimab in cold agglutinin disease. *N Engl J Med*. 2021;384(14):1323-1334.
381. Röth A, Broome CM, Barcellini W, et al. Long-term sutimlimab improves quality of life for patients with cold agglutinin disease: CARDINAL 2-year follow-up. *Blood Adv*. 2023;7(19):5890-5897.
382. Röth A, Barcellini W, D'Sa S, et al. Sustained inhibition of complement C1s with sutimlimab over 2 years in patients with cold agglutinin disease. *Am J Hematol*. 2023;98(8):1246-1253.
383. Röth A, Berentsen S, Barcellini W, D'Sa S, et al. Sutimlimab in patients with cold agglutinin disease: results of the randomized placebo-controlled phase 3 CADENZA trial. *Blood*. 2022;140(9):980-991.
384. Jäger U, Barcellini W, Broome CM, et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: recommendations from the First International Consensus Meeting. *Blood Rev*. 2020 May;41:100648.

PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Fibrinogen Products Prior Authorization Policy
- Fibryga® (fibrinogen [human] intravenous injection – Octapharma)
- RiaSTAP® (fibrinogen concentrate [human] intravenous injection – CSL Behring)

REVIEW DATE: 11/08/2023

OVERVIEW

Fibryga and RiaSTAP, human fibrinogen concentrates, are indicated for treatment of acute bleeding episodes in patients with **congenital fibrinogen deficiency**, including afibrinogenemia and hypofibrinogenemia.[1,2] Both the Fibryga and RiaSTAP prescribing information note that these agents are not indicated for dysfibrinogenemia.

Disease Overview

Congenital deficiencies in fibrinogen (also known as Factor I) can be quantitative or qualitative.[3,4] Quantitative disorders include afibrinogenemia (absence of circulating fibrinogen) and hypofibrinogenemia (low levels of circulating fibrinogen). By contrast, dysfibrinogenemia is a qualitative deficiency in which fibrinogen levels are adequate, but function is impaired. In all cases, clinical presentation is variable; however, bleeding and thromboembolism are possible.

Diagnosis is made by routine coagulation tests in addition to fibrinogen assays.[5] An accurate diagnosis is crucial to distinguish between quantitative and qualitative disorders and guide appropriate treatment. Treatment of fibrinogen deficiency is generally on-demand for acute bleeding episodes, although effective prophylaxis has been used in high-risk patients (e.g., secondary prevention after cerebral hemorrhage, primary prevention during pregnancy to prevent miscarriage).[6,7]

Guidelines

Guidelines are available from the British Committee for Standards in Haemotology (2014); the guideline was written prior to approval of Fibryga.[8] Regarding diagnosis, it is noted that afibrinogenemia and hypofibrinogenemia manifest as prolonged prothrombin time and activated partial thromboplastin time, as well as reduced fibrinogen activity and fibrinogen antigen. Fibrinogen concentrate (e.g., RiaSTAP) may be required to treat or prevent bleeding. Cryoprecipitate is noted to be similarly effective to fibrinogen concentrate but may be associated with transfusion reactions or volume overload.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of fibrinogen products (Fibryga, RiaSTAP). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with fibrinogen products as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Fibryga and RiaSTAP is recommended in those who meet the following criteria:

FDA-Approved Indication

47. Congenital Fibrinogen Deficiency (Factor I Deficiency), Including Afibrinogenemia and Hypofibrinogenemia. Approve for 1 year if the patient meets the following (A and B):

A) The diagnosis is confirmed by the following laboratory testing (i and ii):

- **i.** Prolonged activated partial thromboplastin time and prothrombin time at baseline, as defined by the laboratory reference values; AND
- **ii.** Lower than normal plasma functional and antigenic fibrinogen levels at baseline, as defined by the laboratory reference values; AND

B) The requested agent is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Fibryga and RiaSTAP is not recommended in the following situations:

100. Concomitant Use of Fibryga and RiaSTAP. There are no data to support concomitant use of these products.

101. Dysfibrinogenemia. In dysfibrinogenemia, patients have adequate levels of fibrinogen but dysfunctional clotting.[3,4] Fibryga and RiaSTAP are not indicated in dysfibrinogenemia.[1,2]

102. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

385. RiaSTAP® intravenous injection [prescribing information]. Kankakee, IL: CSL Behring; June 2021.
386. Fibryga® intravenous injection [prescribing information]. Hoboken, NJ: Octapharma; August 2022.
387. De Moerloose P, Casini A, Neerman-Arbez M. Congenital fibrinogen disorders: an update. *Semin Thromb Hemost*. 2013;39(6):585-595.
388. Factor I (Fibrinogen) Deficiency. National Hemophilia Foundation. Available at: https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Other-Factor-Deficiencies/Factor-I. Accessed on November 5, 2023.
389. Casini A, Unda A, Palla R, et al. Diagnosis and classification of congenital fibrinogen disorders: communication from the SSC of the ISTH. *J Thromb Hemost.* 2018;16(9).
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391. Palla R, Peyvandi F, Shapiro AD. Rare bleeding disorders: diagnosis and treatment. *Blood*. 2015;125(13):2052-2061.
392. Mumford AD, Ackroyd S, Alikhan R, et al.; BCSH Committee. Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology. *Br J Haematol*. 2014;167(3):304-26.

PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Gene Therapy – Zynteglo Prior Authorization Policy
- Zynteglo™ (betibeglogene autotemcel intravenous infusion – Bluebird Bio)

REVIEW DATE: 11/01/2023

OVERVIEW

Zyntelgo is an autologous hematopoietic stem cell-based gene therapy indicated for the treatment of adult and pediatric patients with β-thalassemia who require regular red blood cell (RBC) transfusions.[1] The efficacy and safety of Zynteglo in children < 4 years of age have not been established; no data are available in this population. Zynteglo is given as a single dose which contains a minimum of 5.0 x 10^6 CD34+ cells/kg of body weight. The median dose of Zynteglo in the pivotal trials was 9.4 x 10^6 CD34+ cells/kg.

Disease Overview

The condition of β-thalassemia is a group of recessively inherited blood disorders caused by β-globin gene mutations that either reflect a reduced (β^+) or relative lack (β^0) of production of functional β-globin.[2] The attenuated or lack of hemoglobin (Hb) results in chronic anemia of varying degrees of severity and insufficient delivery of oxygen to the body. Those with severe anemia may require lifelong RBC transfusions and regular iron chelation to prevent iron overload. The extremely low Hb levels can lead to many types of symptoms and health-related issues (e.g., dizziness, weakness, fatigue, increased cardiac effort, tachycardia, poor growth) or ineffective erythropoiesis (e.g., bone changes, massive splenomegaly). An estimated 3,000 patients in the US have β-thalassemia and slightly less than one-half of the patients are dependent on RBC transfusions.

Clinical Efficacy

The efficacy of Zynteglo was evaluated in two ongoing, open-label, 2-year, single-arm, Phase III trials that involved patients ≤ 50 years of age with transfusion-dependent β-thalassemia (NORTHSTAR-2 and NORTHSTAR-3) who received one dose of Zynteglo.[1,3] All patients underwent mobilization of stem cells (with granulocyte colony-stimulating factor and Mozobil® [plerixafor subcutaneous injection]) and pre-treatment myeloablative conditioning with busulfan prior to treatment with Zynteglo. NORTHSTAR-2 (n = 23) involved patients who had a non-β^0/β^0 genotype. NORTHSTAR 3 (n = 18) involved patients who had a β^0/β^0 or non-β^0/β^0 genotype. In NORTHSTAR-2, 91% of patients obtained transfusion independence, the primary endpoint. Among the patients who obtained transfusion independence, the median weighted average Hb during transfusion independence was 11.8 g/dL.[1] In NORTHSTAR-3, transfusion independence was achieved by 86% of patients. Among the patients who obtained transfusion independence, the median weighted average Hb during transfusion independence was 10.2 g/dL. The median time for the last RBC transfusion prior to transfusion independence after administration of Zynteglo was slightly under 1 month in both trials. In total, 29 patients from NORTHSTAR-2 and NORTHSTAR 3 enrolled in a long-term extension. Data suggest durable results regarding transfusion independence as these two studies have had follow up for over 24 months.

Guidelines

Guidelines have not addressed Zynteglo post approval in the US. In 2021, the Thalassaemia International Federation published guidelines for the management of transfusion-dependent thalassemia.[4]

- **Chelation therapy** was cited as an effective treatment modality in improving survival, decreasing the risk of heart failure, and decreasing morbidities from transfusion-induced iron overload. The

optimal chelation regimen should be individualized and will vary among patients and their clinical status.

- **Allogeneic hematopoietic stem cell transplant (HSCT)** should be offered to patients with β-thalassemia at an early age, before complications due to iron overload have developed if a human leukocyte antigen (HLA) identical sibling is available. In some clinical circumstances, a matched unrelated donor can be adequate.
- **Reblozyl®** (luspatercept-aamt subcutaneous injection), an erythroid maturation agent, can be considered for patients ≥ 18 years of age who require regular RBC transfusions.
- **Zynteglo**, when available, may be an option for selected patients. Examples include young patients (12 to 17 years of age) with a β^+ genotype who do not have an HLA-compatible sibling donor. Also, Zynteglo can be considered in patients 17 to 55 years of age with a β+ genotype who do not have severe comorbidities and are at risk or ineligible to undergo allogeneic HSCT but can otherwise undergo an autologous gene therapy procedure with an acceptable risk.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zynteglo. Approval is recommended for those who meet the Criteria for the listed indication. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zynteglo as well as the specialized training required for administration of Zynteglo, approval requires Zynteglo to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for one dose per lifetime. The approval duration is 6 months to allow for an adequate time frame to prepare and administer one dose of therapy. For certain criteria, verification is required as noted by **[verification in claims history required]**. In the criteria for Zynteglo, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: females/males are defined as individuals with the biological traits of a woman/man, regardless of the individual's gender identity or gender expression.

All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation. Some clients have elected Embarc Benefit Protection. For these clients, the Medical Director will coordinate with eviCore to ensure the Embarc Benefit Protection portion of the review has been completed. If the Embarc Benefit Protection portion of the review has not been completed, the Medical Director will route to Embarc@eviCore.com prior to completing the review.

Documentation: Documentation is required for use of Zynteglo as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zynteglo is recommended in those who meet the following criteria:

FDA-Approved Indication

48. Beta Thalassemia. Approve a one-time (lifetime) dose if the patient meets the following (A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, and R).

A) Patient is ≥ 4 to ≤ 50 years of age; AND

B) Patient is transfusion dependent defined by meeting one of the following (i or ii) **[documentation required]**:
- **i.** Receipt of transfusions of ≥ 100 mL per kg of body weight of packed red cells per year in the 2 years preceding enrollment **[documentation required]**; OR
- **ii.** Patient has received transfusions eight or more times per year in the 2 years before enrollment **[documentation required]**; AND

C) Patient has one of the following genotypes as confirmed by DNA analysis (i or ii) **[documentation required]**:
- **i.** Non-β^0/β^0 genotype **[documentation required]**; OR
  Note: Examples include β^0/β^+, β^E/β^0, and β^+/β^+.
- **ii.** β^0/β^0 genotypes **[documentation required]**; AND
  Note: Other examples include $\beta^0/\beta^{+(IVS\text{-}I\text{-}110)}$ and $\beta^{+(IVS\text{-}I\text{-}110)}/\beta^{+(IVS\text{-}I\text{-}110)}$.

D) Patient does not currently have an active bacterial, viral, fungal, or parasitic infection; AND

E) According to the prescribing physician, hematopoietic stem cell transplantation is appropriate for the patient; AND

F) Patient meets all of the following (i, ii, iii, iv, and v)
- **i.** Patient will undergo mobilization, apheresis, and myeloablative conditioning; AND
- **ii.** The prescribing physician confirms that the hemoglobin level is or will be ≥ 11.0 g/dL within 30 days prior to the following clinical scenarios (a and b):
  - **a)** Prior to mobilization; AND
  - **b)** Before myeloablative conditioning; AND
- **iii.** A granulocyte-colony stimulating factor product and a hematopoietic stem cell mobilizer will be utilized for mobilization; AND
  Note: Filgrastim products are examples of a granulocyte-colony stimulator factor therapy and Mozobil (plerixafor subcutaneous injection) is an example of a hematopoietic stem cell mobilizer.
- **iv.** Busulfan will be used for myeloablative conditioning; AND
- **v.** Patient meets both of the following (a and b):
  - **a)** Patient is not receiving iron chelation therapy or this therapy will be stopped at least 7 days prior to myeloablative conditioning; AND
    Note: Examples of iron chelators used for this condition include deferoxamine injection; deferiprone tablets or solution; and deferasirox tablets.
  - **b)** Use of iron chelators will be avoided for 6 months after infusion of Zynteglo; AND

G) Patient has received or is planning to receive prophylaxis for hepatic veno-occlusive disease/hepatic sinusoidal obstruction syndrome before myeloablative conditioning with busulfan; AND
Note: Examples of medications used include ursodeoxycholic acid or Defitelio (defibrotide intravenous infusion).

H) Females* of reproductive potential must have the prescribing physician confirm the following (i and ii):
- **i.** A negative serum pregnancy test was or will be obtained prior to the start of mobilization and re-confirmed prior to conditioning procedures, as well as before Zynteglo administration; AND
- **ii.** The patient will use an effective method of contraception from the start of mobilization through at least 6 months after administration of Zynteglo; AND

I) Males* must have the prescribing physician confirm that the patient will be using an effective method of contraception from the start of mobilization through at least 6 months after administration of Zynteglo; AND

J) Prior to collection of cells for manufacturing, screening is negative for the following (i and ii):
- **i.** Human T-lymphotropic virus 1 and 2 **[documentation required]**; AND
- **ii.** Human immunodeficiency virus 1 and 2 **[documentation required]**; AND

K) Patient meets one of the following (i or ii):
- **i.** Patients ≥ 16 years of age have a Karnofsky performance status score of ≥ 80 **[documentation required]**; OR
- **ii.** Patients < 16 years of age have a Lansky performance status score of ≥ 80 **[documentation required]**; AND

L) Patient meets both of the following (i and ii):
- **i.** Within 30 days before intended receipt of Zynteglo, the white blood cell count was ≥ 3 x 10^9/L **[documentation required]**; AND
- **ii.** Within 30 days before intended receipt of Zynteglo, the platelet count was ≥ 100 x 10^9/L **[documentation required]**; AND

M) Patient meets both of the following (i and ii):
- **i.** Patient has been evaluated for the presence of severe iron overload **[documentation required]**; AND
- **ii.** Patient does not have evidence of severe iron overload; AND
  Note: Examples of severe iron overload could include abnormal myocardial iron results (a T2*-weighted magnetic resonance imaging measurement of myocardial iron of less than 10 msec); high liver iron concentration (≥ 15.5 mg/g); liver biopsy results suggest abnormalities; or clinical evidence of organ damage (e.g., endocrine comorbidities).

N) Patient does not have any of the following (i, ii, iii, iv, v, and vi):
- **i.** Prior or current malignancy or myeloproliferative disorder; AND
  Note: This does not include adequately treated cone biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin.
- **ii.** Familial cancer syndrome or a history of such in their immediate family; AND
- **iii.** An estimated glomerular filtration rate of < 70 mL/min/1.73 m^2 **[documentation required]**; AND
- **iv.** Uncorrected bleeding disorder; AND
- **v.** A diffusion capacity of carbon monoxide < 50% of predicted **[documentation required]**; AND
- **vi.** Advanced liver disease; AND
  Note: Examples include evidence of cirrhosis and/or persistent alanine aminotransferase, aspartate aminotransferase, or direct bilirubin values greater than three times the upper limit of normal; AND

O) Patient meets one of the following (i or ii):
- **i.** Patient does not have a Human Leukocyte Antigen (HLA)-Matched Family Donor; OR
- **ii.** Patient has a Human Leukocyte Antigen (HLA)-Matched Family Donor but the individual is not able or is unwilling to donate; AND

P) Patient has not received Zynteglo in the past **[verification in claims history required]**; AND
Note: Verify through claims that the patient has not previously received Zynteglo AND, if no claim for Zynteglo is present, the prescribing physician confirms that the patient has not previously received Zynteglo.

Q) Medication is prescribed by a hematologist and/or a stem cell transplant specialist; AND

R) Zynteglo is given as a single dose which contains a minimum of 5.0 x 10^6 CD34+ cells/kg of body weight.

* Refer to the Policy Statement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zynteglo is not recommended in the following situations:

103. Concurrent Use with Reblozyl (luspatercept-aamt subcutaneous injection). Reblozyl was not utilized with Zynteglo in the pivotal trials.

104. Prior Hematopoietic Stem Cell Transplantation.

Note: Prescribing physician must confirm that the patient has not received a prior hematopoietic stem cell transplantation.

Patients who had received a prior hematopoietic stem cell transplantation were not allowed to participate in the pivotal clinical trials involving Zynteglo.

105. Prior Receipt of Gene Therapy. Prior receipt of gene therapy was a reason for patient exclusion in the two pivotal trials.

106. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Pyrukynd Prior Authorization Policy
- Pyrukynd® (mitapivat tablets – Agios)

REVIEW DATE: 03/22/2023

OVERVIEW

Pyrukynd, a pyruvate kinase activator, is indicated for the treatment of **hemolytic anemia due to pyruvate kinase deficiency** in adults.[1]

It is recommended to discontinue Pyrukynd if no benefit has been observed by 24 weeks as evaluated by hemoglobin and hemolysis laboratory results and transfusion requirements.

Disease Overview

Pyruvate kinase deficiency is a rare (three to nine cases per one million people), autosomal recessive enzyme defect in red cells that is caused by mutations in the pyruvate kinase liver and red blood cell (*PKLR*) gene.[2,3] These alterations result in a deficit of pyruvate kinase activity in red cells which leads to hemolytic anemia of varying severity.[2] Other complications include iron overload (and its sequelae), bilirubin gallstones, pulmonary hypertension, thrombosis, and extramedullary hematopoiesis. Commonly present are compound heterozygous mutations in the gene encoding the L and R isozymes of *PKLR* with more than 300 mutations noted; most patients have at least on missense mutation. More notable management strategies involve blood transfusions, splenectomy, and chelation therapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Pyrukynd. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Pyrukynd as well as the monitoring required for adverse events and long-term efficacy, Pyrukynd approval requires Pyrukynd to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Pyrukynd as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Pyrukynd is recommended in those who meet the following criteria:

FDA-Approved Indication

49. Hemolytic Anemia Due to Pyruvate Kinase Deficiency. Approve for the duration noted below if the patient meets one of the following criteria (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND
ii. Patient meets both of the following (a and b):
  a) Presence of at least two variant/mutant alleles in the pyruvate kinase liver and red blood cell (*PKLR*) gene **[documentation required]**; AND
  b) At least one of the variant/mutant alleles was a missense variant **[documentation required]**; AND
iii. Patient meets one of the following (a or b):
  a) Patient has a current hemoglobin level ≤ 10 g/dL; OR
  b) Patient is currently receiving red blood cell transfusions regularly, defined as at least six transfusions within the last year; AND
iv. Medication is prescribed by or in consultation with a hematologist.

B) Patient is Currently Receiving Pyrukynd. Approve for 1 year if the patient meets the following (i, ii, iii, iv, and v):
i. Patient is ≥ 18 years of age; AND
ii. Patient meets both of the following (a and b):
  a) Presence of at least two variant/mutant alleles in the pyruvate kinase liver and red blood cell (*PKLR*) gene **[documentation required]**; AND
  b) At least one of the variant/mutant alleles was a missense variant **[documentation required]**; AND
iii. Patient has a current hemoglobin level ≤ 12.0 g/dL; AND
iv. According to the prescriber, the patient has experienced a benefit from therapy based one of the following (a, b, or c):
  a) Increase in or maintenance of hemoglobin levels; OR
  b) Improvement in or maintenance of hemolysis laboratory parameters; OR
  Note: Examples of laboratory parameters that are markers of hemolysis include indirect bilirubin, lactate dehydrogenase, and haptoglobin.
  c) Decrease in or maintenance of transfusion requirements; OR
v. Medication is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Pyrukynd is not recommended in the following situations:

107. Patient with Pyruvate Kinase Deficiency Homozygous for the c.1436G>A (p.R479H) Variant/Mutation in the Pyruvate Kinase Liver and Red Blood Cell (*PKLR*) Gene. Such patients were excluded from the pivotal studies investigating Pyrukynd in patients with pyruvate kinase deficiency because they did not achieve a hemoglobin response in the dose-ranging study.[1]

108. Patient with Pyruvate Kinase Deficiency with Two Non-Missense Variants/Mutations (without the presence of another missense variant/mutation) in the Pyruvate Kinase Liver and Red Blood Cell (*PKLR*) Gene. Such patients were excluded from the pivotal studies investigating Pyrukynd because they did not achieve a hemoglobin response in the dose-ranging study.[1]

109. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Reblozyl Prior Authorization Policy
- Reblozyl® (luspatercept-aamt subcutaneous injection – Celgene/Bristol Myers Squibb)

REVIEW DATE: 12/20/2023

OVERVIEW

Reblozyl, an erythroid maturation agent, is indicated for the following conditions:[1]

- **Beta thalassemia**, for the treatment of adults with anemia who require regular red blood cell (RBC) transfusions.
- **Myelodysplastic syndromes (MDS)**, very low to intermediate-risk, for the treatment of adults who may require regular RBC transfusions with anemia without previous erythropoiesis-stimulating agent (ESA) use (ESA-naïve).
- **MDS with ring sideroblasts**, very low- to intermediate-risk disease, or with **myelodysplastic/myeloproliferative neoplasm** (MDS/MPN) with ring sideroblasts and thrombocytosis for the treatment of anemic adults who have failed an ESA and require two or more RBC units over 8 weeks.

Clinical Efficacy

Beta Thalassemia

In the BELIEVE trial, all patients required regular RBC transfusions at baseline, defined as at least six units of packed RBCs in the preceding 24 weeks, with no transfusion-free intervals > 35 days in that timeframe.[1,2] A response to Reblozyl was defined as a 33% reduction in transfusion requirement from pretreatment baseline and a reduction in transfusion requirements of at least two RBC units during Weeks 13 through 24 compared with pretreatment baseline. The percentage of patients who had a reduction in the transfusion burden of at least 33% from baseline during Weeks 13 through 24 plus a reduction of at least two RBC units over this 12-week interval was greater for patients given Reblozyl (21.4%) vs. patients given placebo (4.5%) [P < 0.001].

MDS or MDS/MPN

In the MEDALIST trial, patients were required to have ring sideroblasts according to World Health Organization criteria (i.e., ≥ 15% or ≥ 5% if *SF3B1* mutation was present).[1,3] Patients with deletion 5q [del(5q)] were excluded from enrollment. All patients were required to have disease refractory or unlikely to respond to ESAs (unless endogenous erythropoietin level was elevated), and the median pretransfusion hemoglobin level was 7.6 g/dL (range 5 to 10 g/dL). Patients had to require RBC transfusions (two or more RBC units over 8 weeks). During the initial 24 weeks of the trial, 58% of patients had transfusion independence for 8 weeks or longer compared with 13% of patients in the placebo group.[1] In the pivotal MEDALIST trial publication, which primarily involved patients with MDS, improvements in hemoglobin from baseline were sustained through at least Week 25. It is notable that the MDS disease course may evolve over time and potentially lead to loss of response of previously effective agents; thus, close follow-up is appropriate to verify that therapeutic response is maintained.

COMMANDS was an open-label trial that compared Reblozyl with epoetin alfa in patients with very low, low, or intermediate risk MDS or with MDS/MPN with ring sideroblasts and thrombocytosis.[1,4] Patients were required to have had two to six RBC units in 8 weeks and erythropoietin levels < 500 U/L at screening. The primary endpoint was RBC transfusion independence for at least 12 weeks with a concurrent mean

hemoglobin increase of at least 1.5 g/dL during Weeks 1 to 24 which was met by 58.5% of patients in the Reblozyl group vs. 31.2% of patients in the epoetin alfa group.

Dosing Information

For all indications, the starting dose is 1 mg/kg given subcutaneously once every 3 weeks.[1] Assess and review hemoglobin levels and transfusion record prior to each dose. Discontinue if a patient does not experience a decrease in transfusion burden after 9 weeks of treatment (administration of three doses) at the maximum dose level. For beta thalassemia, the maximum recommended dose is 1.25 mg/kg given once every 3 weeks. For MDS and MDS/MPN, the maximum dose is 1.75 mg/kg given once every 3 weeks.

Guidelines

The Thalassaemia International Federation published guidelines for the management of transfusion-dependent thalassemia (2021).[5]

- **Chelation therapy** was cited as an effective treatment modality in improving survival, decreasing the risk of heart failure, and decreasing morbidities from transfusional-induced iron overload. The optimal chelation regimen should be individualized and will vary among patients and their clinical status.
- **Allogeneic hematopoietic stem cell transplant (HSCT)** should be offered to patients with beta thalassemia at an early age, before complications due to iron overload have developed if a human leukocyte antigen (HLA) identical sibling is available. In some clinical circumstances, a matched unrelated donor can be adequate.
- **Reblozyl** can be considered for patients ≥ 18 years of age who require regular RBC transfusions.
- **Zynteglo™** (betibeglogene autotemcel intravenous infusion), a gene therapy, may be an option for selected patients when available. Examples include young patients (12 to 17 years of age) with a β^+ genotype who do not have an HLA-compatible sibling donor. Also, Zynteglo can be considered in patients 17 to 55 years of age with a β^+ genotype who do not have severe comorbidities and are at risk or ineligible to undergo allogeneic HSCT but can otherwise undergo an autologous gene therapy procedure with an acceptable risk.

The National Comprehensive Cancer Network guidelines for MDS (version 3.2023 – November 10, 2023) recommend Reblozyl in the following situations:[6]

- **MDS:** Treatment with Reblozyl is supported for lower-risk disease associated with symptomatic anemia with no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts ≥ 15% (or ring sideroblasts ≥ 5% with an *SF3B1* mutation) as a single agent (category 1). Treatment with Reblozyl is supported for lower-risk disease associated with symptomatic anemia with no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts < 15% (or ring sideroblasts < 5% with an *SF3B1* mutation) and serum erythropoietin levels ≤ 500 mU/L as a single agent or following no response to an ESA (despite adequate iron stores) [category 2A].
- **MDS/MPN:** Treatment with Reblozyl can be considered for MDS/MPN with an *SF3B1* mutation and thrombocytosis as a single agent (category 2B). Reblozyl can also be used for wild-type *SF3B1* if the patient has thrombocytosis and ring sideroblasts ≥ 15% [category 2B].

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Reblozyl. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Reblozyl as well as the monitoring required for adverse events and long-term efficacy, approval requires Reblozyl to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Reblozyl is recommended in those who meet one of the following criteria:

FDA-Approved Indications

50. Beta Thalassemia. Approve for the duration noted if the patient meets one of the following (A or B):

- **A)** Initial Therapy. Approve for 4 months if the patient meets all the following (i, ii, iii, and iv):
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** According to the prescriber, the patient requires regular red blood cell transfusions as defined by meeting both of the following (a and b):
    - **a)** Patient has received at least 6 units of packed red blood cells within the preceding 24 weeks; AND
    - **b)** Patient has not had any transfusion-free period > 35 days within the preceding 24 weeks; AND
  - **iii.** Patient has not received Zynteglo (betibeglogene autotemcel intravenous infusion) in the past; AND
  - **iv.** The medication is being prescribed by or in consultation with a hematologist.
- **B)** Patient is Currently Receiving Reblozyl. Approve for 1 year if the patient meets all the following (i and ii):
  - **i.** According to the prescriber, the patient has experienced a clinically meaningful decrease in transfusion burden as defined by a decrease of at least 2 units in red blood cell transfusion burden over the past 6 months compared with the pretreatment baseline (prior to the initiation of Reblozyl); AND
  - **ii.** Patient has not received Zynteglo (betibeglogene autotemcel intravenous infusion) in the past.

51. Myelodysplastic Syndrome. Approve for the duration noted if the patient meets one of the following (A or B):

- **A)** Initial Therapy. Approve for 6 months if the patient meets all of the following (i, ii, iii, iv, v, vi, vii, and viii):
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** According to the prescriber, the patient has myelodysplastic syndromes and meets one of the following (a or b):
    - **a)** Ring sideroblast positivity; OR
      Note: This is defined as ring sideroblasts ≥ 15% or ring sideroblasts ≥ 5% with an *SF3B1* mutation.
    - **b)** Serum erythropoietin level is ≤ 500 mU/mL; AND
  - **iii.** Patient has very low- to intermediate-risk myelodysplastic syndromes, as determined by the prescriber; AND
    Note: This is determined using the International Prognostic Scoring System (IPSS).
  - **iv.** Patient does not have a confirmed mutation with deletion 5q [del(5q)]; AND

v. Patient currently requires blood transfusions, defined as at least two red blood cell units over the previous 8 weeks; AND
vi. Pretreatment hemoglobin level is < 10.0 g/dL; AND
vii. Reblozyl will not be used in combination with an erythropoiesis stimulating agent; AND
viii. The medication is being prescribed by or in consultation with an oncologist or hematologist.

B) Patient is Currently Receiving Reblozyl. Approve for 6 months if, according to the prescriber, the patient has experienced a clinically meaningful decrease in transfusion burden or the hemoglobin level has increased by ≥ 1.5 g/dL compared with the pretreatment baseline.

3. Myelodysplastic/Myeloproliferative Neoplasm. Approve for the duration noted if the patient meets one of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets all of the following (i, ii, iii, iv, v, vi, vii, and viii):
i. Patient is ≥ 18 years of age; AND
ii. According to the prescriber, the patient has myelodysplastic/myeloproliferative neoplasm and meets both of the following (a and b):
a) Ring sideroblast positivity; AND
Note: This is defined as ring sideroblasts ≥ 15% or ring sideroblasts ≥ 5% with an *SF3B1* mutation.
b) Thrombocytosis defined as platelet count ≥ 450 x 10^9/L; AND
iii. Patient has very low- to intermediate-risk disease, as determined by the prescriber; AND
Note: This is determined using the International Prognostic Scoring System (IPSS).
iv. Patient does not have a confirmed mutation with deletion 5q [del(5q)]; AND
v. Patient currently requires blood transfusions, defined as at least two red blood cell units over the previous 8 weeks; AND
vi. Pretreatment hemoglobin level is < 10.0 g/dL; AND
vii. Reblozyl will not be used in combination with an erythropoiesis stimulating agent; AND
viii. The medication is being prescribed by or in consultation with an oncologist or hematologist.

B) Patient is Currently Receiving Reblozyl. Approve for 1 year if, according to the prescriber, the patient has experienced a clinically meaningful decrease in transfusion burden or the hemoglobin level has increased by ≥ 1.5 g/dL compared with the pretreatment baseline.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Reblozyl is not recommended in the following situations:

110. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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401. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 3.2023 – November 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 13, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Ryplazim Prior Authorization Policy
- Ryplazim® (plasminogen, human-tvmh intravenous infusion – Prometic/Kedrion)

REVIEW DATE: 01/03/2024

OVERVIEW

Ryplazim, a plasma-derived human plasminogen, is indicated for the treatment of **plasminogen deficiency type 1 (hypoplasminogenemia)**.[1]

Disease Overview

Congenital plasminogen deficiency is an ultra-rare, autosomal recessive disease affecting approximately 500 patients in the US (estimated prevalence of 1.6 per million individuals).[2] Female predominance has been reported. The median age of first clinical manifestations has been reported as approximately 10 months in one case series.[3] Type 1 deficiency is considered "true" plasminogen deficiency and results in decreased plasminogen antigen and activity levels. Type 2 deficiency is referred to as dysplasminogenemia; plasminogen antigen levels are normal, but functional activity is reduced. Type 2 deficiency is asymptomatic and not clinically relevant. By contrast, type 1 deficiency may present with multisystem disease characterized by fibrin-rich ("woody") pseudomembranes on mucous membranes.[2] Treatment of congenital plasminogen deficiency should be coordinated by a hematologist who is knowledgeable about the disorder.[4]

Clinical Efficacy

Clinical efficacy of Ryplazim was evaluated in one Phase II/III pivotal study in patients with plasminogen deficiency type 1 (n = 15).[1,5] All patients had a baseline plasminogen activity level between < 5% and 45% of normal, as well as biallelic mutations in the *PLG* (plasminogen) gene.[1] The primary clinical efficacy endpoint was overall clinical success. Overall clinical success was defined as 50% of patients with visible or other measurable lesions achieving at least a 50% improvement in lesion number/size or functionality impact from baseline. Patients were not required to have active lesions at baseline; however, they were required to have a history of lesions and symptoms consistent with a diagnosis of congenital plasminogen deficiency. Among the 15 patients in the study, a total of 32 external lesions and 12 internal lesions were evaluated. The majority of lesions were resolved by Week 48; no patients experienced new or recurrent lesions.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ryplazim. All approvals are provided for the duration noted below. In cases where the approval duration is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ryplazim as well as the monitoring required for adverse events and long-term efficacy, approval requires Ryplazim to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ryplazim is recommended in those who meet the following criteria:

FDA-Approved Indication

52. Plasminogen Deficiency Type 1 (Hypoplasminogenemia). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following (i, ii, and iii):

i. Patient has a diagnosis of plasminogen deficiency type 1 confirmed by both of the following:

a) Biallelic mutations in the *PLG* gene; AND

b) Baseline plasminogen activity level (prior to initiating Ryplazim) ≤ 45% of normal based on the reference range for the reporting laboratory; AND

ii. Patient has a history of lesions and symptoms consistent with a diagnosis of congenital plasminogen deficiency; AND

iii. Ryplazim is prescribed by or in consultation with a hematologist.

B) Patient is Currently Receiving Ryplazim. Approve for 1 year if the patient meets the following (i and ii):

i. Patient meets ONE of the following (a or b):

a) Patient has had a clinical response to Ryplazim, as determined by the prescriber; OR
Note: Examples of clinical response include resolution of active lesions, stabilization of current lesions, and prevention of new or recurrent lesions.

b) Patient has a trough plasminogen activity level ≥ 10% (absolute change in plasminogen activity) above the baseline trough level (prior to initiating Ryplazim); AND

ii. Ryplazim is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ryplazim is not recommended in the following situations:

111. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Tretten Prior Authorization Policy
- Tretten® (coagulation Factor XIII A-Subunit [recombinant] intravenous infusion – NovoNordisk)

REVIEW DATE: 11/08/2023

OVERVIEW

Tretten, a coagulation Factor XIII A-Subunit, is indicated for routine prophylaxis of bleeding in patients with congenital factor XIII A-subunit deficiency.[1] The agent is not indicated for use in patients with congenital Factor XIII B-subunit deficiency.

Disease Overview

Congenital Factor XIII deficiency is caused by defects in both Factor XIIIA and Factor XIIIB genes.[2,3] However, most cases are due to genetic alterations on the Factor XIIIA gene. The estimated prevalence of Factor XIIIA deficiency is one case in 1 to 2 million people. Clinical symptoms include delayed wound healing, bleeding of soft and subcutaneous tissue, recurrent spontaneous miscarriage, and central nervous system (CNS) bleeding, which may be life-threatening. If patients have severe Factor XIII deficiency, early manifestations include bleeding from the umbilical cord or CNS. Prospective data showed that a level of 30% Factor XIII clotting activity is an adequate therapeutic target for most patients. Treatment of Factor XIII deficiency involves use of fresh frozen plasma, cryoprecipitate, Corifact® (Factor XIII concentration intravenous infusion), or Tretten.

Guidelines

The National Bleeding Disorders Foundation Medical and Scientific Advisory Council has guidelines for the treatment of hemophilia and other bleeding disorders (revised August 2023).[4] Tretten is recommended in patients who have factor XIII deficiency who lack the factor XIII-A subunit. It will not work in patients who only lack factor XIII-B subunit.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tretten. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tretten as well as the monitoring required for adverse events and long-term efficacy, approval requires Tretten to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tretten is recommended for patients who meet the following criteria:

FDA-Approved Indication

53. Congenital Factor XIII A-Subunit Deficiency. Approve for 1 year if the agent is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tretten is not recommended in the following situations:

112. Congenital Factor XIII B-Subunit Deficiency. Tretten will not work in patients who only lack Factor XIII-B subunit.[1,2]

113. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Vonvendi Prior Authorization Policy
- Vonvendi® (von Willebrand factor [recombinant] intravenous infusion – Baxalta)

REVIEW DATE: 11/08/2023

OVERVIEW

Vonvendi, a recombinant von Willebrand factor (VWF), is indicated for use in adults ≥ 18 years of age diagnosed with von Willebrand disease (VWD) for:[1]

- **On-demand treatment and control** of bleeding episodes.
- **Perioperative management** of bleeding.
- **Routine prophylaxis to reduce the frequency of bleeding episodes in patients with severe Type 3 VWD** receiving on-demand therapy.

Disease Overview

VWD is an inherited bleeding disorder caused by a deficiency or impairment of a protein found in blood called VWF.[4-6] VWF is a plasma protein with a dual role in hemostasis by mediating platelet adhesion at sites of vascular injury and by binding and stabilizing Factor VIII. The disease is rather common as it affects 1 in 100 people; both genders are impacted equally. Symptoms of VWD include mucocutaneous bleeding and excessive hemorrhage following invasive procedures; occasionally, soft tissue hematomas and joint bleeding may also occur. Women who have VWD may experience heavy menorrhagia or experience excessive bleeding at childbirth. Bleeding episodes may be life-threatening in patients with severe forms of VWD. VWD is classified into six types (1, 2A, 2B, 2M, 2N, and 3) according to distinct genotypic, clinical, and laboratory phenotypic characteristics. Type 1 VWD is the most common type (60% to 80% of patients) and represents a partial quantitative deficiency of VWF. Bleeding symptoms are generally mild to moderate. Type 2 VWD affects 15% to 30% of patients and consists of four disease subtypes (2A, 2B, 2M, and 2N) dependent on the specific gene mutation (e.g., decreased VWF-dependent platelet adhesion, decreased binding affinity for Factor VIII). This type is due to a qualitative VWF defect, and the bleeding is generally moderate, but can vary among patients. Type 3 VWD is uncommon (5% to 10% of patients) but is usually severe because it is due to a virtually complete deficiency of VWF. Many patients with VWD also have reduced Factor VIII levels. Treatment options for VWD include desmopressin either parenterally or by a highly concentrated nasal spray (Stimate), Vonvendi, or plasma-derived Factor VIII product that contain VWF.

Guidelines

The National Bleeding Disorders Foundation Medical and Scientific Advisory Council has guidelines for the treatment of hemophilia and other bleeding disorders (revised August 2023).[3] Most patients with type 1 VWD may be treated with a desmopressin product (DDAVP injection or Stimate nasal spray). Some patients with type 2A VWD may respond to DDAVP; a clinical trial with DDAVP should be performed to determine if DDAVP can be used for these particular patients. The guidelines recommend that both DDAVP injection and Stimate not be used in children aged < 2 years and in patients with VWD in whom desmopressin does not provide adequate VWF levels. Also, they should be used cautiously in pregnant women during labor and delivery. Use of plasma-derived VWF-containing Factor VIII concentrates that have VWF is recommended in certain types of VWD that do not respond to therapy with desmopressin (i.e., type 2B VWD and type 3 VWD). Also, plasma-derived Factor VIII concentrates that contain VWF are recommended in types 1, 2A, 2M, and 2N VWD who have become transiently unresponsive to DDAVP, as well as in surgical situations, especially in young children < 2 years of age. Alphanate, Humate-P, and

Wilate are indicated for use in VWD; in certain patients Koāte® (antihemophilic Factor [plasma-derived] intravenous infusion) may also be effective. Use of cryoprecipitate is not recommended as it has not undergone any viral attenuation steps. Cryoprecipitate should not be utilized to treat patients with VWD except in life- and limb-threatening emergencies when VWD-containing factor VIII concentrate is not immediately available. Vonvendi is available to treat patients with Type 2B and Type 3 VWD; it can also be used in patients with Types 1, 2A, 2M, and 2N VWD who are not responsive to DDAVP and in children < 2 years of age, regardless of VWD type. Vonvendi is approved for use as routine prophylaxis only in patients with severe Type 3 VWD who were previously treated with VWF (recombinant or plasma-derived) on demand. It is produced in Chinese hamster ovary cells and it does not contain human or animal-derived proteins in its cell culture or in its final formulation (a third generation product). Vonvendi contains ultra-large VWF multimers, in addition to the high, medium, and low molecular weight VWF multimers normally found in plasma. Trace amounts of recombinant Factor VIII is in the product as well.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vonvendi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vonvendi as well as the monitoring required for adverse events and long-term efficacy, approval requires Vonvendi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vonvendi is recommended in those who meet the following criteria:

FDA-Approved Indication

2. Von Willebrand Disease. Approve for 1 year if the agent is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vonvendi is not recommended in the following situations:

114. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Hemophilia – Altuviiio Prior Authorization Policy
- Altuviiio™ (antihemophilic factor [recombinant] Fc-VWF-XTEN fusion protein-ehtl intravenous injection – Bioverativ/Sanofi)

REVIEW DATE: 03/29/2023

OVERVIEW

Altuviiio, a recombinant DNA-derived Factor VIII concentrate, is indicated for use in hemophilia A in adults and children for:[1]

- **Routine prophylaxis** to reduce the frequency of bleeding episodes.
- **On-demand treatment and control** of bleeding episodes.
- **Perioperative management** of bleeding.

It is notable that Altuviiio has demonstrated a 3- to 4-fold prolonged half-life relative to other standard and extended half-life products.[1]

Disease Overview

Hemophilia A is an X-linked bleeding disorder primarily impacting males caused by a deficiency in Factor VIII.[2-5] In the US, the incidence of hemophilia A in males is 1:5,000 with an estimated 20,000 people in the US living with hemophilia A. The condition is characterized by bleeding in joints, either spontaneously or in a provoked joint by trauma. Bleeding can occur in many different body areas as well (e.g., muscles, central nervous system). The bleeding manifestations can lead to substantial morbidity such as hemophilic arthropathy. Disease severity is usually defined by the plasma levels or activity of Factor VIII classified as follows: severe (levels < 1% of normal), moderate (levels 1% to 5% of normal), and mild (levels > 5% to < 40% of normal); phenotypic expression may vary. Approximately 50% of patients with hemophilia A are categorized as having severe disease.

Guidelines

Guidelines have not addressed Altuviiio. Guidelines for hemophilia from the National Hemophilia Foundation (March 2022)[6] and the World Federation of Hemophilia (2020)[7] recognize the important role of Factor VIII products and Hemlibra® (emicizumab-kxwh subcutaneous injection) in the management of hemophilia A in patients.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Altuviiio. All approvals are provided for the duration noted below. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Altuviiio, as well as the monitoring required for adverse events and long-term efficacy, the agent is required to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Altuviiio is recommended in those who meet the following criteria:

FDA-Approved Indication

54. Hemophilia A. Approve for 1 year if the patient meets one of the following criteria (A or B):

- **A)** Initial Therapy. Approve if the patient meets the following (i, ii, and iii):
  - **i.** Altuviiio is being used in at least one of the following scenarios (a, b, or c):
    - **a)** Routine prophylaxis; OR
    - **b)** On-demand treatment and control of bleeding episodes; OR
    - **c)** Perioperative management of bleeding; AND
  - **ii.** Patient meets both of the following (a and b):
    - **a)** Factor VIII inhibitor testing has been performed within the last 30 days; AND
    - **b)** Patient does not have a positive test for Factor VIII inhibitors ≥ 0.6 Bethesda units/mL; AND
  - **iii.** Medication is prescribed by or in consultation with a hemophilia specialist.
- **B)** Patient Currently Receiving Altuviiio or Has Received Altuviiio in the Past. Approve if the patient meets the following (i, ii, and iii):
  - **i.** Altuviiio is being used in at least one of the following scenarios (a, b, or c):
    - **a)** Routine prophylaxis; OR
    - **b)** On-demand treatment and control of bleeding episodes; OR
    - **c)** Perioperative management of bleeding; AND
  - **ii.** Patient meets one of the following (a or b):
    - **a)** Patient meets both of the following [(1) and (2)]:
      - **(1)** Factor VIII inhibitor testing has been performed within the last 30 days; AND
      - **(2)** Patient does not have a positive test for Factor VIII inhibitors ≥ 0.6 Bethesda units/mL; OR
    - **b)** According to the prescribing physician, patient does not have clinical manifestations suggesting the presence of Factor VIII inhibitors; AND
      Note: Inhibitors may be present if bleeding is not well controlled, there is decreased responsiveness to Factor VIII therapy, and/or if expected Factor VIII activity plasma levels are not achieved.
  - **iii.** Medication is prescribed by or in consultation with a hemophilia specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Altuviiio is not recommended in the following situations:

115. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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6. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders (Revised March 2022). MASAC Document #272. Adopted on April 27, 2022.

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PRIOR AUTHORIZATION POLICY

POLICY: Hemophilia – Eptacog Products – NovoSeven RT Prior Authorization Policy
- NovoSeven® RT (coagulation Factor VIIa [recombinant] intravenous infusion – Novo Nordisk)

REVIEW DATE: 11/08/2023

OVERVIEW

NovoSeven RT is indicated for the treatment of bleeding episodes and perioperative management in the following conditions:

- **Congenital Factor VII deficiency** in adults and children;
- **Glanzmann's thrombasthenia** with refractoriness to platelet transfusions in adults and children, with or without antibodies to platelets;
- **Hemophilia, acquired** in adults; and
- **Hemophilia A or B with inhibitors** in adults and children.[1]

Of note, off-label use of NovoSeven RT in the general population has been suggested in a variety of acute bleeding scenarios (e.g., trauma, intracranial hemorrhage). A 2012 Cochrane Review concluded that the effectiveness of recombinant activated Factor VIIa as a general hemostatic drug in non-hemophiliac patients remains unproven and that use outside its licensed indications should be limited to clinical trials.[2] Various reviews and clinical practice guidelines concur that the evidence is insufficient to support use of NovoSeven RT as a hemostatic agent outside of its labeled uses.[3-5]

Guidelines

The National Bleeding Disorders Foundation Medical and Scientific Advisory Council (MASAC) guidelines (updated August 2023) support NovoSeven RT as a treatment option for inherited **hemophilia A or B with inhibitors**, **acquired hemophilia A** (other forms of acquired hemophilia not addressed), and **Factor VII deficiency**.[6] Glanzmann's thrombasthenia is not addressed in the guideline. MASAC recommendations (2013) also state that recombinant Factor VIIa has demonstrated efficacy and safety for prophylactic use for patients with inhibitors in hemophilia A and hemophilia B.[7]

Regarding **hemophilia A and B with inhibitors**, World Federation of Hemophilia guidelines (2020) support recombinant Factor VIIa for patients with high-titer inhibitors who require acute treatment or around surgery/invasive procedures.[8] For low-titer inhibitors, Factor VIII or IX replacement may be used. These products may also be used for patients with a history of a high-titer inhibitor whose titer has fallen to low or undetectable levels. However, once an anamnestic response occurs, further treatment with Factor replacement is typically no longer effective, and bypass agent therapy (e.g., recombinant Factor VIIa) is needed. National Hemophilia Foundation MASAC guidelines (updated August 2020) have similar recommendations: treatment for patients with inhibitors depends on multiple factors, including type of inhibitor (high- or low-responding), current titer, location of bleed, and previous response.[6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of NovoSeven RT. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with NovoSeven RT as well as the monitoring required for adverse events and

long-term efficacy, approval requires NovoSeven RT to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of NovoSeven RT is recommended in those who meet one of the following criteria:

FDA-Approved Indications

55. Congenital Factor VII Deficiency. Approve for 1 year if NovoSeven RT is prescribed by or in consultation with a hemophilia specialist.

56. Glanzmann's Thrombasthenia. Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient is refractory to platelet transfusions; AND
- **B)** The medication is prescribed by or in consultation with a hematologist.

57. Hemophilia, Acquired. Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The medication is prescribed by or in consultation with a hemophilia specialist.

58. Hemophilia A with Inhibitors. Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient meets one of the following (i, ii, or iii):
  - **i.** Patient has a positive inhibitor titer ≥ 5 Bethesda Units; OR
  - **ii.** Patient has a history of an inhibitor with anamnestic response to Factor VIII replacement therapy, which, according to the prescriber, precludes the use of Factor VIII replacement to treat bleeding episodes; OR
  - **iii.** Patient has a history of an inhibitor with refractory hemostatic response to increased Factor VIII dosing, which, according to the prescriber, precludes the use of Factor VIII replacement to treat bleeding episodes; AND
- **B)** The medication is prescribed by or in consultation with a hemophilia specialist.

59. Hemophilia B with Inhibitors. Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient meets one of the following (i, ii, or iii):
  - **i.** Patient has a positive inhibitor titer ≥ 5 Bethesda Units; OR
  - **ii.** Patient has a history of an inhibitor with anamnestic response to Factor IX replacement therapy, which, according to the prescriber, precludes the use of Factor IX replacement to treat bleeding episodes; OR
  - **iii.** Patient has a of an inhibitor with refractory hemostatic response to increased Factor IX dosing, which, according to the prescriber, precludes the use of Factor IX replacement to treat bleeding episodes; AND
- **B)** The medication is prescribed by or in consultation with a hemophilia specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of NovoSeven RT is not recommended in the following situations:

116. Bleeding Associated with Liver Disease. Randomized trials have failed to show benefit of NovoSeven RT in controlling upper gastrointestinal bleeding and variceal bleeding in patients with advanced liver disease.[9,10] American Association for the Study of Liver Disease guidelines for portal hypertensive bleeding in cirrhosis (2016) state that recombinant Factor VIIa should not be used to correct coagulopathy in this scenario.[11]

117. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Hemophilia – Eptacog Products – Sevenfact Prior Authorization Policy
- Sevenfact® (Factor VIIa [recombinant]-jncw intravenous infusion – LFB S.A./Hema Biologics)

REVIEW DATE: 11/08/2023

OVERVIEW

Sevenfact, a recombinant Factor VIIa product, is indicated for the treatment and control of bleeding episodes occurring in adults and adolescents (≥ 12 years of age) with **hemophilia A or B with inhibitors**.[1] As a limitation of use, Sevenfact is not indicated for the treatment of patients with congenital Factor VII deficiency.

Disease Overview

In hemophilia A and B, antibodies to exogenous clotting factor, known as "inhibitors", may develop. Approximately 30% of patients with severe hemophilia A and up to 5% of patients with severe hemophilia B develop inhibitors to Factor VIII or Factor IX during their lifetime.[2] A high-responding inhibitor (≥ 5 Bethesda Units [BU]) tends to persist, whereas low-responding inhibitors of < 5 BU may wane without changes to the treatment regimen. Presence of inhibitors is associated with higher disease burden, increased risk of musculoskeletal complications, pain, physical limitations, and treatment challenges.[2,3]

Guidelines

National Bleeding Disorders Foundation MASAC guidelines (revised August 2023) recognize both Sevenfact and NovoSeven RT® (coagulation Factor VIIa [recombinant] intravenous infusion) as treatments for **hemophilia A or B with inhibitors**.[4] No preference is stated for one agent over the other. It is noted that choice of product depends on multiple factors, including type of inhibitor (low- or high-responding), current titer, location of bleed, and previous response. Of note, NovoSeven RT, but <u>not</u> Sevenfact, is recognized as a treatment option in other settings, such as acquired hemophilia A and congenital Factor VII deficiency.

World Federation of Hemophilia (WFH) guidelines (2020) support recombinant Factor VIIa for patients with high-titer inhibitors who require acute treatment or around surgery/invasive procedures.[3] For low-titer inhibitors, Factor VIII or IX replacement may be used. These products may also be used for patients with a history of a high-titer inhibitor whose titer has fallen to low or undetectable levels. However, once an anamnestic response occurs, further treatment with Factor replacement is typically no longer effective, and bypass agent therapy (e.g., recombinant Factor VIIa) is needed.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Sevenfact. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sevenfact as well as the monitoring required for adverse events and long-term efficacy, approval requires Sevenfact to be prescribed by or in consultation with a physician who specializes in the condition being treated.

<u>Automation</u>: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sevenfact is recommended in those who meet one of the following criteria:

FDA-Approved Indications

60. Hemophilia A with Inhibitors. Approve for 1 year if the patient meets all of the following (A, B, and C):
- **A)** Patient is ≥ 12 years of age; AND
- **B)** Patient meets one of the following (i, ii, or iii):
  - **i.** Patient has a positive inhibitor titer ≥ 5 Bethesda Units; OR
  - **ii.** Patient has a history of anamnestic response to Factor VIII replacement therapy, which, according to the prescriber, precludes the use of Factor VIII replacement to treat bleeding episodes; OR
  - **iii.** Patient has a history of refractory response to increased Factor VIII dosing, which, according to the prescriber, precludes the use of Factor VIII replacement to treat bleeding episodes; AND
- **C)** The medication is prescribed by or in consultation with a hemophilia specialist.

61. Hemophilia B with Inhibitors. Approve for 1 year if the patient meets all of the following (A, B, and C):
- **A)** Patient is ≥ 12 years of age; AND
- **B)** Patient meets one of the following (i, ii, or iii):
  - **i.** Patient has a positive inhibitor titer ≥ 5 Bethesda Units; OR
  - **ii.** Patient has a history of anamnestic response to Factor IX replacement therapy, which, according to the prescriber, precludes the use of Factor IX replacement to treat bleeding episodes; OR
  - **iii.** Patient has a of refractory response to increased Factor IX dosing, which, according to the prescriber, precludes the use of Factor IX replacement to treat bleeding episodes; AND
- **C)** The medication is prescribed by or in consultation with a hemophilia specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sevenfact is not recommended in the following situations:

118. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Hemophilia – FEIBA Prior Authorization Policy
- Hemophilia – FEIBA® (anti-inhibitor coagulant complex intravenous infusion – Baxalta/Takeda)

REVIEW DATE: 11/08/2023

OVERVIEW

FEIBA, a human plasma fraction with Factor VIII bypassing activity, is indicated for use in **hemophilia A and B patients with inhibitors** for control and prevention of bleeding episodes, perioperative management, and routine prophylaxis to prevent or reduce the frequency of bleeding episodes.[1] It contains both activated and inactivated forms of Factors II, VII, IX, and X and is thus referred to as activated prothrombin complex concentrate (aPCC).[1,2] FEIBA is produced from pooled human plasma.[1]

Guidelines

Regarding **hemophilia A with inhibitors** and **hemophilia B with inhibitors** (without history of anaphylaxis/allergy to Factor IX), World Federation of Hemophilia guidelines (2020) support aPCC for patients with high-titer inhibitors who require acute treatment or around surgery/invasive procedures.[3] For low-titer inhibitors, Factor VIII or IX replacement may be used. These products may also be used for patients with a history of a high-titer inhibitor whose titer has fallen to low or undetectable levels. However, once an anamnestic response occurs, further treatment with Factor replacement is typically no longer effective, and bypass agent therapy (e.g., aPCC) is needed. National Bleeding Disorders Foundation Medical and Scientific Advisory Council (MASAC) guidelines (updated August 2023) have similar recommendations: treatment for patients with inhibitors depends on multiple factors, including type of inhibitor (high- or low-responding), current titer, location of bleed, and previous response.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of FEIBA. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with FEIBA as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of FEIBA is recommended in those who meet one of the following criteria:

FDA-Approved Indications

62. Hemophilia A with Inhibitors. Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient meets one of the following (i, ii, or iii):
  - **i.** Patient has a positive inhibitor titer ≥ 5 Bethesda Units; OR

ii. Patient has a history of an inhibitor with anamnestic response to Factor VIII replacement therapy, which, according to the prescriber, precludes the use of Factor VIII replacement to treat bleeding episodes; OR

iii. Patient has a history of an inhibitor with refractory hemostatic response to increased Factor VIII dosing, which, according to the prescriber, precludes the use of Factor VIII replacement to treat bleeding episodes; AND

B) The medication is prescribed by or in consultation with a hemophilia specialist.

63. Hemophilia B with Inhibitors. Approve for 1 year if the patient meets the following (A and B):

A) Patient meets one of the following (i, ii, or iii):

i. Patient has a positive inhibitor titer ≥ 5 Bethesda Units; OR

ii. Patient has a history of an inhibitor with anamnestic response to Factor IX replacement therapy, which, according to the prescriber, precludes the use of Factor IX replacement to treat bleeding episodes; OR

iii. Patient has a of an inhibitor with refractory hemostatic response to increased Factor IX dosing, which, according to the prescriber, precludes the use of Factor IX replacement to treat bleeding episodes; AND

B) The medication is prescribed by or in consultation with a hemophilia specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of FEIBA is not recommended in the following situations:

119. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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433. National Bleeding Disorders Foundation. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and selected disorders of the coagulation system (August 2023). MASAC Document #280. Available at: https://www.hemophilia.org/sites/default/files/document/files/MASAC-Products-Licensed.pdf. Accessed on November 5, 2023.

434. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia*. 2020;26 Suppl 6:1-158.

PRIOR AUTHORIZATION POLICY

POLICY: Hemophilia Factor IX Products Prior Authorization Policy

EXTENDED HALF-LIFE RECOMBINANT PRODUCTS

- Alprolix® (Coagulation Factor IX [recombinant] Fc fusion protein intravenous infusion – Bioverativ)
- Idelvion (Coagulation Factor IX [recombinant] albumin fusion protein intravenous infusion – CSL Behring)
- Rebinyn® (Coagulation Factor IX [recombinant] glycoPEGylated intravenous infusion – NovoNordisk)

Standard Half-Life Recombinant Products

- BeneFIX® (Coagulation Factor IX [recombinant] intravenous infusion – Wyeth/Pfizer)
- Ixinity® (Coagulation Factor IX [recombinant] intravenous infusion – Medexus)
- Rixubis® (Coagulation Factor IX [recombinant] intravenous infusion – Baxalta)

Plasma-Derived Products

- AlphaNine® SD (Coagulation Factor IX [plasma-derived] intravenous infusion – Grifols)
- Mononine® (Coagulation Factor IX [plasma-derived] intravenous infusion – CSL Behring)
- Profilnine® (Factor IX Complex [plasma-derived] intravenous infusion – Grifols)

REVIEW DATE: 03/22/2023

OVERVIEW

Alprolix, Idelvion, and Rebinyn are extended half-life recombinant Factor IX products; BeneFIX, Ixinity and Rixubis are standard half-life recombinant Factor IX products; and AlphaNine SD, Mononine, and Profilnine are plasma-derived Factor IX products.[1-9] All agents are indicated in various clinical scenarios for use in the management of patients with hemophilia B.

Profilnine is also used in patients with Factor II and/or X deficiency.[10] Some data are available, albeit limited.

Disease Overview

Hemophilia B is a recessive X-linked bleeding disorder caused by mutations in the factor IX gene that leads to the deficiency or absence of the coagulation factor IX.[11-13] It occurs in 1 out of 30,000 male births and affects about 5,000 people in the US. Hemophilia B predominantly occurs in males; however, approximately 10% of females are carriers and are at risk of usually mild bleeding. The severity of bleeding depends on the degree of the factor IX defect and the phenotypic expression. Factor levels of <1%, 1% to 5%, and > 5% to < 40% are categorized as severe, moderate, and mild hemophilia B, respectively. Patients with mild hemophilia B may only experience abnormal bleeding during surgery, during tooth extractions, or when injured. Patients with moderate hemophilia B generally have prolonged bleeding responses to minor trauma. Severe hemophilia B is marked by spontaneous bleeding such as spontaneous hemarthrosis, soft-tissue hematomas, retroperitoneal bleeding, intracerebral hemorrhage, and delayed bleeding post-surgery. Complications from recurrent bleeding and soft-tissue hematomas include severe arthropathy, and joint contractures, which may lead to pain and disability. The main treatment of hemophilia B is replacement of missing blood coagulation factor with Factor IX products. Factor IX replacement therapy may be used on-demand when bleeding occurs or given as routine prophylaxis with scheduled infusions. Both plasma-derived and recombinant Factor IX products are available. In general, prophylactic therapy

has been associated with a reduction in bleeds and improved outcomes for selected patients (e.g., patients with moderate or severe factor IX deficiency). The goal of therapy is to prevent uncontrolled internal hemorrhage and severe joint damage, and to properly manage bleeding episodes. The development of inhibitors occurs at a lower frequency in patients with severe hemophilia B compared with severe hemophilia A but can occur in up to 5% of patients. Higher doses than that typically used for the uses of standard half-life products can be given if the patient develops an inhibitor.

Guidelines

Guidelines for hemophilia from the National Hemophilia Foundation (2022)[14] and the World Federation of Hemophilia (2020)[15] recognize the important role of Factor IX products in the management of hemophilia B patients.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of the following Factor IX products: Alprolix, Idelvion, Rebinyn, BeneFIX, Ixinity, Rixubis, AlphaNine, Mononine, and Profilnine. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with recombinant Factor IX products, as well as the monitoring required for adverse events and long-term efficacy, the agent is required to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Alprolix, Idelvion, Rebinyn, BeneFIX, Ixinity, and Rixubis is recommended for patients who meet the following criteria:

FDA-Approved Indication

64. Hemophilia B. Approve for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

II. Coverage of AlphaNine SD, Mononine, and Profilnine is recommended for patients who meet the following criteria:

FDA-Approved Indication

1. Hemophilia B. Approve for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

III. Coverage of Profilnine is also recommended for patients who meet the following criteria:

Other Uses with Supportive Evidence

2. Factor II Deficiency. Approve Profilnine for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

3. Factor X Deficiency. Approve Profilnine for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of the cited Factor IX products is not recommended in the following situations:

120. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Alprolix® intravenous infusion [prescribing information]. Waltham, MA: Bioverativ; October 2020.
2. Idelvion® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; July 2021.
3. Rebinyn® intravenous infusion [prescribing information]. Plainsboro, NJ: Novo Nordisk; August 2022.
4. BeneFIX® intravenous infusion [prescribing information]. Philadelphia, PA: Wyeth/Pfizer; November 2022.
5. Ixinity® intravenous infusion [prescribing information]. Chicago, IL: Medexus; November 2022.
6. Rixubis® intravenous infusion [prescribing information]. Lexington, MA: Baxalta; June 2020.
7. AlphaNine® SD intravenous infusion [prescribing information]. Los Angeles, CA: Grifols; March 2021.
8. Mononine® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; December 2018.
9. Profilnine® intravenous infusion [prescribing information]. Los Angeles, CA: Grifols; March 2021.
10. Menegatti M, Peyvandi F. Treatment of rare factor deficiencies other than hemophilia. *Blood*. 2019;133(5):415-424.
11. Sidonio RF, Malec L. Hemophilia B (Factor IX Deficiency). *Hematol Oncol Clin North Am*. 2021;35(6):1143-1155.
12. Mancuso ME, Mahlangu JN, Pipe SW. The changing treatment landscape in haemophilia: from standard half-life clotting factor concentrates to gene editing. *Lancet*. 2021;397:630-640.
13. Croteau SE. Hemophilia A/B. *Hematol Oncol Clin N Am*. 2022;36:797-812.
14. National Hemophilia Foundation. Medical and Scientific Advisory Council (MASAC) recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders (Revised March 2022). MASAC document #272. Available at: https://www.hemophilia.org/sites/default/files/document/files/272._Treatment.pdfAccessed on March 14, 2023.
15. Srivastava A, Santagostino E, Dougall A, on behalf of the WFH guidelines for the management of hemophilia panelists and co-authors. Guidelines for the management of hemophilia, 3rd edition. *Haemophilia*. 2020;26(Suppl 6):1-158.

PRIOR AUTHORIZATION POLICY

POLICY: Hemophilia – Factor VIII Products

Extended Half-Life Products

- Adynovate® (Antihemophilic Factor PEGylated intravenous infusion – Baxalta)
- Eloctate® (Antihemophilic Factor Fc fusion protein intravenous infusion – Bioverativ)
- Esperoct® (Antihemophilic factor glycopegylated intravenous infusion – Novo Nordisk)
- Jivi® (Antihemophilic Factor PEGylated-aucl intravenous infusion – Bayer HealthCare)

Standard Half-Life Products

- Advate® (Antihemophilic Factor intravenous infusion – Baxalta)
- Afstyla® (Antihemophilic Factor single chain intravenous infusion – CSL Behring)
- Kogenate® FS (Antihemophilic Factor intravenous infusion – Bayer HealthCare)
- Kovaltry® (Antihemophilic Factor intravenous infusion – Bayer HealthCare)
- Novoeight® (Antihemophilic Factor intravenous infusion – Novo Nordisk)
- Nuwiq® (Antihemophilic Factor intravenous infusion – Octapharma)
- Recombinate® (Antihemophilic Factor intravenous infusion –Baxalta)
- Xyntha®/Xyntha® Solofuse™ (Antihemophilic Factor intravenous infusion, plasma/albumin-free – Wyeth/Pfizer)

Plasma-Derived Standard Half-Life Products without Von Willebrand Factor

- Hemofil® M (Antihemophilic Factor intravenous infusion –Baxalta)

Plasma-Derived Standard Half-Life Products with Von Willebrand Factor

- Alphanate® (Antihemophilic Factor/von Willebrand Factor Complex [human] intravenous infusion – Grifols)
- Humate-P® (Antihemophilic Factor/von Willebrand Factor Complex intravenous infusion – CSL Behring)
- Koāte® (Antihemophilic Factor intravenous infusion – Grifols/Kedrion Biopharma)
- Wilate® (von Willebrand Factor/Coagulation Factor VIII Complex intravenous infusion – Octapharma)

REVIEW DATE: 03/22/2023; selected revision 04/05/2023

OVERVIEW

For the **management of hemophilia A**, many recombinant Factor VIII products are available, including extended half-life products[1-4] (Adynovate, Eloctate, Esperoct, and Jivi) as well as standard half-life products (Advate, Afstyla, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, and Xyntha).[5-13] In general, these products are utilized in various clinical scenarios in the management of patients with hemophilia A. Several standard half-life Factor VIII plasma-derived products are available. Hemofil M is a plasma-derived standard half-life product that does not contain substantial amounts of von Willebrand Factor which is indicated for use in the management of hemophilia A.[14] Plasma-derived Factor VIII products that contain von Willebrand Factor include Alphanate, Humate P, Koate, and Wilate.[15-18] Alphanate, Humate P, and Wilate are indicated for use in clinical scenarios for the management of hemophilia A, as well as in patients with von Willebrand disease (VWD).[15,16,18] Wilate is the only agent FDA-approved for use in routine prophylaxis in children 6 years of age and older and adults with VWD.[18] However, the other agents have been used in this clinical scenario as well.[29] Koate is indicated for the control and prevention of bleeding episodes or in order to perform emergency elective surgery in patients with hemophilia A.[17] This policy

does not include Altuviiio™ (antihemophilic factor [recombinant] Fc-VWF-XTEN fusion protein-ehtl intravenous injection).[19]

Disease Overview

Hemophilia A is an X-linked bleeding disorder primarily impacting males caused by a deficiency in Factor VIII.[20-24] In the US, the incidence of hemophilia A in males is 1:5,000 with an estimated 20,000 people in the US living with hemophilia A. The condition is characterized by bleeding in joints, either spontaneously or in a provoked joint. Bleeding can occur in many different body areas as well (e.g., muscles, central nervous system). The bleeding manifestations can lead to substantial morbidity such as hemophilic arthropathy. Disease severity is usually defined by the plasma levels or activity of Factor VIII classified as follows: severe (levels < 1% of normal), moderate (levels 1% to 5% of normal), and mild (levels > 5% to < 40% of normal); phenotypic expression may vary. Approximately 50% of patients with hemophilia A are categorized as having severe disease which may require routine prophylactic Factor VIII therapy.

VWD is a group of inherited bleeding disorders related to defects of von Willebrand Factor (vWF), which is needed to achieve hemostasis.[25-27] It occurs equally in males and females. The disease leads to bleeding from impaired platelet adhesion and aggregation, which may be accompanied by reduced levels of factor VIII. Mucous membrane and skin bleeding symptoms, as well as bleeding with surgical or other hematostatic challenges, may occur. The prevalence of the disease is approximately 1.3%. Pregnancy can increase vWF levels and confound the diagnosis. The three major subtypes of VWD include: partial quantitative vWF deficiency (type 1, 75% of patients); qualitative vWF deficiency (type 2, 25% of patients); and complete vWF deficiency (type 3, rare). Type 2 disease is further divided into four variants (2A, 2B, 2M, 2N) on the basis of the phenotype. In type 3 VWD, Factor VIII levels are usually very low. Acquired von Willebrand syndrome may result but is rare, occurring in fewer than one in 100,000 adults. The bleeding risk varies between modest increases in bleeding which occur only with procedures to a major risk of spontaneous hemorrhage. Approaches to the management of VWD involve increasing plasma concentrations of vWF through stimulation with desmopressin; replacing vWF by using human plasma-derived viral inactivated concentrates; and promoting hemostasis by use of hemostatic agents with mechanisms other than increasing vWF; and Vonvendi® (von Willebrand factor [recombinant] intravenous infusion). Regular prophylaxis is not frequently required.

Guidelines

Guidelines for hemophilia from the National Hemophilia Foundation (2022)[20] and the World Federation of Hemophilia (2020)[28] recognize the important role of Factor VIII products in the management of hemophilia A. Also, Factor VIII products that contain vWF have a role in the management of VWD.[23]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of the following Factor VIII products: Adynovate, Eloctate, Esperoct, Jivi, Advate, Afstyla, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, Xyntha, Hemofil M, Alphanate, Humate-P, Koate, and Wilate. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with recombinant Factor VIII products, as well as the monitoring required for adverse events and long-term efficacy, the agent is required to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Adynovate, Eloctate, Esperoct, Jivi, Advate, Afstyla, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, and Xyntha is recommended in those who meet the following criteria:

FDA-Approved Indication

65. Hemophilia A. Approve the requested agent for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

II. Coverage of Hemofil M and Koate is recommended in those who meet the following criteria:

FDA-Approved Indication

1. Hemophilia A. Approve the requested agent for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

III. Coverage of Alphanate, Humate-P, and Wilate is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Hemophilia A. Approve the requested agent for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

2. Von Willebrand Disease. Approve for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of the cited Factor VIII products is not recommended in the following situations:

121. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

435. Adynovate® intravenous infusion [prescribing information]. Lexington, MA: Baxalta; June 2021.
436. Eloctate® intravenous infusion [prescribing information]. Waltham, MA: Bioverativ; December 2020.
437. Jivi® intravenous infusion [prescribing information]. Whippany, NJ: Bayer; August 2018.
438. Esperoct® intravenous infusion [prescribing information]. Plainsboro, NJ: Novo Nordisk; August 2022.
439. Advate® intravenous infusion [prescribing information]. Westlake Village, CA: Baxalta/Shire; December 2018.
440. Kovaltry® intravenous infusion [prescribing information]. Whippany, NJ: Bayer; December 2022.
441. Afstyla® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; April 2021.
442. Kogenate® FS lyophilized powder for reconstitution for intravenous infusion [prescribing information]. Whippany, NJ: Bayer; December 2019.
443. Novoeight® intravenous infusion [prescribing information]. Plainsboro, NJ: Novo Nordisk; July 2020.
444. Nuwiq® intravenous infusion [prescribing information]. Paramus, NJ: Octapharma; June 2021.
445. Recombinate™ intravenous infusion [prescribing information]. Lexington, MA: Baxalta; June 2021.
446. Xyntha® intravenous infusion [prescribing information]. Philadelphia, PA: Wyeth/Pfizer; July 2022.
447. Xyntha® Solofuse™ intravenous infusion [prescribing information]. Philadelphia, PA: Wyeth/Pfizer; July 2022.
448. Hemofil® M intravenous infusion [prescribing information]. Lexington, MA: Baxalta; June 2018.
449. Alphanate® intravenous infusion [prescribing information]. Los Angeles, CA: Grifols; March 2021.
450. Humate-P® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; June 2020.

451. Koāte® intravenous infusion [prescribing information]. Fort Lee, NJ and Research Triangle Park, NC: Kedrion and Grifols; June 2018.
452. Wilate® intravenous infusion [prescribing information]. Hoboken, NJ: Octapharma; December 2023.
453. Altuviiio™ intravenous infusion [prescribing information]. Waltham, MA: Bioverativ/Sanofi; February 2023.
454. National Hemophilia Foundation. Medical and Scientific Advisory Council (MASAC) recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders (Revised March 2022). MASAC document #272. Available at: https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-272-masac-recommendations-concerning-products-licensed-for-the-treatment-of-hemophilia-and-other-bleeding-disorders. Accessed on March 13, 2023.
455. Mancuso ME, Mahlangu JN, Pipe SW. The changing treatment landscape in haemophilia: from standard half-life clotting factor concentrates to gene editing. *Lancet*. 2021;397:630-640.
456. Croteau SE. Hemophilia A/B. *Hematol Oncol Clin North Am*. 2022;36(4):797-812.
457. Franchini M, Mannucci PM. The more recent of hemophilia treatment. *Semin Thromb Hemost*. 2022;48(8):904-910.
458. Peyvandi F, Garagiola I, Young G. The past and future of haemophilia: diagnosis, treatments and its complications. *Lancet*. 2016;388(10040):187-197.
459. Neff AT, Sidonio RF. Management of VWD. *Hematology Am Soc Hematol Educ Program*. 2014;(1):536-541.
460. Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (vWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel Report (USA). *Haemophilia*. 2008;14(2):171-232.
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463. Franchini M, Seidizadeh O, Mannucci PM. Prophylactic management of patients with von Willebrand disease. *Ther Adv Hematol*. 2021;12:1-12.

PRIOR AUTHORIZATION POLICY

POLICY: Hemophilia – Gene Therapy – Hemgenix Prior Authorization Policy
- Hemgenix® (etranacogene dezaparvovec-drlb intravenous infusion – CSL Behring and uniQure)

REVIEW DATE: 01/11/2023

OVERVIEW

Hemgenix, an adeno-associated virus vector-based gene therapy, is indicated for the treatment of adults with hemophilia B (congenital Factor IX deficiency) who: 1) currently use Factor IX prophylaxis therapy; or 2) have current or historical life-threatening hemorrhage; or 3) have repeated, serious spontaneous bleeding episodes.[1]

Disease Overview

Hemophilia B is a genetic bleeding disorder caused by missing or insufficient levels of blood Factor IX, a protein required to produce blood clots to halt bleeding.[2-5] The condition is a rare X-linked bleeding disorder that mainly impacts males. Hemophilia B is four times less common than hemophilia A, which is caused by a relative lack of blood Factor VIII. Approximately 30,000 individuals are living with hemophilia in the US and hemophilia B accounts for around 15% to 20% of hemophilia cases, or around 6,000 patients. Symptoms patients may experience include heavy or prolonged bleeding following an injury or after a medical procedure. Bleeding can also occur internally into joints, muscles or internal organs. Spontaneous bleeding events may also occur. Complications in patients with hemophilia B include joint disease and hemarthrosis. Hemophilia B may be diagnosed when bleeding occurs in infancy or later in life for those with milder disease. There is a strong correlation between Factor IX levels and phenotypic expression of bleeding. Normal plasma levels of Factor IX range from 50% to 150%. The disease is classified based on reduced levels. Mild, moderate, and severe hemophilia B are characterized by Factor IX levels ranging from 6% up to 49%, 1% up to 5%, and < 1%, respectively. Besides Hemgenix, Factor IX products, both recombinant and plasma-derived, are used routinely to prevent bleeding or are given on demand to treat bleeding episodes associated with hemophilia B.

Clinical Efficacy

The efficacy of Hemgenix was evaluated in a prospective, open-label, single-dose, single-arm, multinational pivotal study called HOPE-B that involved 54 adult male patients with moderately severe or severe hemophilia B (Factor IX levels $\leq 2\%$).[1,6-9] Patients prospectively completed a lead-in period of at least 6 months in which standard care routine Factor IX prophylaxis therapy was given.[1] This was followed by a single intravenous dose of 2×10^{13} genome copies/kg of body weight of Hemgenix. Patients were permitted to continue Factor IX prophylaxis during Months 0 to 6 after dosing, if needed, until Factor IX levels were adequate. The estimated mean annualized bleeding rate during Months 7 to 18 following Hemgenix treatment was 1.9 bleeds/year compared with 4.1 bleeds/year during the lead-in period (before Hemgenix administration).[1,6-9] The HOPE-B trial is ongoing.[1] Other data are also available.[10-12]

Safety

Monitor patients during administration of Hemgenix and for at least 3 hours after the end of the infusion for infusion reactions. Closely monitor transaminase levels at least once per week for 3 months after Hemgenix administration to assess for the risk of potential hepatotoxicity. Consider corticosteroid treatment if elevations occur. Monitor Factor IX activity and for Factor IX inhibitors.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Hemgenix. Because of the specialized skills required for evaluation and diagnosis of patients treated with Hemgenix as well as the monitoring required for adverse events and long-term efficacy, approval requires Hemgenix to be prescribed by or in consultation with a physician who specializes in the condition being treated. For certain criteria, verification is required as noted by **[verification required by prescriber]**. All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation. In the approval indication for Hemgenix, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Hemgenix is recommended in those who meet the following criteria:

FDA-Approved Indication

66. Hemophilia B. Approve a one-time per lifetime dose if the patient meets the following criteria (A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, and Q):

- **A)** Patient is male*; AND
- **B)** Patient is greater than or equal to 18 years of age; AND
- **C)** Patient has moderately severe or severe hemophilia B as evidence by a baseline (without Factor IX replacement therapy) Factor IX level of ≤ 2% of normal **[documentation required]**; AND
- **D)** Patient meets one of the following (i, ii, or iii):
  - **i.** Patient meets both of the following: (a and b):
    - **a)** Patient has been receiving routine prophylaxis with Factor IX therapy continuously for at least 2 months **[documentation required]**; AND
    - **b)** According to the prescribing physician, the patient has a history of use of Factor IX therapy for at least 150 exposure days; OR
  - **ii.** Patient meets both of the following (a and b):
    - **a)** Patient has a history of life-threatening hemorrhage; AND
    - **b)** On-demand use of Factor IX therapy was required for this life-threatening hemorrhage; OR
  - **iii.** Patient meets both of the following (a and b):
    - **a)** Patient has a history of repeated, serious spontaneous bleeding episodes; AND
    - **b)** On-demand use of Factor IX therapy was required for these serious spontaneous bleeding episodes; AND
- **E)** Patient meets all of the following criteria (i, ii, and iii):
  - **i.** Factor IX inhibitor titer testing has been performed within 30 days before receipt of Hemgenix **[documentation required]**; AND
  - **ii.** Patient does not currently have an inhibitor to Factor IX **[documentation required]**; AND
  - **iii.** Patient does not have a history of Factor IX inhibitors **[documentation required]**; AND
- **F)** Prescriber attests that prophylactic therapy with Factor IX will not be given after Hemgenix administration once adequate Factor IX levels have been achieved; AND

Note: Use of episodic Factor IX therapy is acceptable for the treatment of bleeds and for surgery/procedures if needed as determined by the hemophilia specialist physician.

G) Patient has not received Hemgenix in the past **[verification required by prescriber]**; AND
Note: Verify through claims history that the patient has not previously received Hemgenix AND, if no claim for Hemgenix is present, the prescriber must attest that the patient has not previously received Hemgenix.

H) Patient must meet both of the following (i and ii):
- **i.** Patient does not have an active infection with hepatitis B virus or hepatitis C virus **[documentation required]**; AND
- **ii.** Patient is not currently receiving antiviral therapy for a prior hepatitis B virus or C virus exposure **[documentation required]**; AND

I) Patient does not have uncontrolled human immunodeficiency virus **[documentation required]**; AND
Note: A patient testing positive for human immunodeficiency virus can still qualify for Hemgenix if controlled on antiviral therapy with CD4+ counts ≥ 200/µL or by a viral load of ≤ 200 copies/mL.

J) Patient has undergone a liver health assessment within the last 30 days and meets all of the following (i, ii, iii, and iv):
- **i.** Alanine aminotransferase is ≤ 2 times the upper limit of normal **[documentation required]**; AND
- **ii.** Aspartate aminotransferase is ≤ 2 times the upper limit of normal **[documentation required]**; AND
- **iii.** Total bilirubin levels are ≤ 2 times the upper limit of normal **[documentation required]**; AND
- **iv.** Alkaline phosphatase levels are ≤ 2 times the upper limit of normal **[documentation required]**; AND

K) Patient does not have evidence of advanced liver impairment and/or advanced fibrosis **[documentation required]**; AND
Note: For example, liver elastrography (e.g., ≥ 9 kPA) suggestive of or equal to METAVIR Stage 3 disease.

L) Within the last 30 days, platelet counts were evaluated and were ≥ 50 x 10^9/L **[documentation required]**; AND

M) Patient has adequate renal function as defined by meeting both of the following (i and ii):
- **i.** Patient has an estimated creatinine clearance ≥ 30 mL/min **[documentation required]**; AND
- **ii.** Creatinine levels are ≤ 2 times the upper limit of normal **[documentation required]**; AND

N) Physician attests that the patient does not have another coagulation disorder, besides hemophilia B; AND

O) Following Hemgenix infusion, the physician attests that the following will be performed (i, ii, and iii):
- **i.** Patient meets both of the following (a and b):
  - **a)** Liver enzyme testing to monitor for liver enzyme elevations will be done at least weekly for the first 3 months and periodically thereafter; AND
  - **b)** Implementing a course of corticosteroids will be considered if the patient experiences clinically relevant increases in alanine aminotransferase levels; AND
- **ii.** Patient will undergo monitoring for Factor IX activity at least weekly for the first 3 months and periodically thereafter; AND
- **iii.** Patients with preexisting risk factors for hepatocellular carcinoma will receive abdominal ultrasound screenings and be monitored at least annually for alpha fetoprotein elevations in the 5 years following receipt of Hemgenix; AND
  Note: Risk factors include a patient with prior of hepatitis B and/or C, non-alcoholic fatty liver disease, chronic alcohol consumption, non-alcoholic steatohepatitis, and advanced age.

P) Medication is prescribed by a physician who specializes in hemophilia; AND

Q) If criteria A through P are met, approve one dose (kit) of Hemgenix to provide for a one time (per lifetime) dose of 2 x 10^{13} genome copies based on current body weight in kg (within the past 30 days) **[documentation required]** by intravenous infusion. Table 1 provides the kit size and the National Drug Codes (NDCs).

***** Refer to the Policy Statement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Hemgenix is not recommended in the following situations:

122. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

Table 1. Hemgenix Multi-Vial Kits.[1]
NDC – National Drug Code.

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PRIOR AUTHORIZATION POLICY

POLICY: Hemophilia – Gene Therapy – Roctavian Prior Authorization Policy
- Roctavian® (valoctocogene roxaparvovec-rvox intravenous infusion – BioMarin)

REVIEW DATE: 08/16/2023

OVERVIEW

Roctavian, an adeno-associated virus vector-based gene therapy, is indicated for the treatment of adults with severe hemophilia A (congenital Factor VIII deficiency with Factor VIII activity < 1 IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test.[1]

Disease Overview

Hemophilia A is an X-linked bleeding disorder primarily impacting males caused by a deficiency in Factor VIII.[2-7] In the US, the incidence of hemophilia A in males is 1:5,000 with an estimated 20,000 people in the US living with hemophilia A. The condition is characterized by bleeding in joints, either spontaneously or in a provoked joint. Bleeding can occur in many different body areas as well (e.g., muscles, central nervous system). The bleeding manifestations can lead to substantial morbidity such as hemophilic arthropathy. Disease severity is usually defined by the plasma levels or activity of Factor VIII classified as follows: severe (< 1 IU/dL), moderate (1 IU/dL to 5 IU/dL), and mild (> 5 IU/dL to < 40 IU/dL); phenotypic expression may vary. Approximately 50% of patients with hemophilia A are categorized as having severe disease. These patients usually require routine prophylaxis with Factor VIII replacement therapy products or Hemlibra® (emicizumab subcutaneous injection) to prevent bleeding.

Clinical Efficacy

The efficacy of Roctavian was evaluated in one open-label, single-group, multinational Phase III trial (GENEr8-1) involving 134 adult males (≥ 18 years of age) with severe hemophilia A (Factor VIII activity level ≤ 1 IU/dL).[1,8,9] Patients involved in the trial did not have Factor VIII inhibitors (or a history of such inhibitors) and were receiving regular prophylaxis with Factor VIII products. Use of prophylactic Factor VIII therapy was not permitted during the trial, but could be used up to 4 weeks post Roctavian administration to allow the agent to have an effect. Other notable exclusion criteria were active infection, chronic or active hepatitis B or C, immunosuppressive disorder (including HIV), Stage 3 or 4 liver fibrosis, cirrhosis, liver function test abnormalities, a history of thrombosis or thrombophilia, serum creatinine ≥ 1.4 mg/dL, and active malignancy. Patients had to be treated or exposed to Factor VIII concentrates previously for a minimum of 150 exposure days. Use of systemic immunosuppressive agents (not including corticosteroids), or live vaccines within 30 days before Roctavian infusion prevented participation. In the 132 patients who completed more than 51 weeks of follow-up (and were HIV-negative), the mean Factor VIII activity level at Weeks 49 through 52 had increased by 41.9 IU/dL (a non-hemophilic range). Among the 112 patients enrolled from a noninterventional study who had baseline annualized bleeding rate information prospectively collected for at least 6 months before receiving Roctavian (the rollover population), the mean annualized rates of Factor VIII concentrate use and treated bleeding after Week 4 had decreased after Roctavian administration by 98.6% and 83.8%, respectively ($P < 0.001$ for both comparisons). At Year 3 post Roctavian dosing the mean annualized bleeding rate in the rollover population in the efficacy evaluation period was 2.6 bleeds/year compared to a mean baseline of 5.4 bleeds/year (while using Factor VIII therapies); mean Factor VIII activity levels were 21 IU/dL at this timepoint (mild hemophilic range).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Roctavian. Because of the specialized skills required for evaluation and diagnosis of patients treated with Roctavian as well as the monitoring required for adverse events and long-term efficacy, approval requires Roctavian to be prescribed by a physician who specializes in the condition being treated. For certain criteria, verification is required as noted by **[verification in claims history required]**. For the dosing criteria, verification of the appropriate weight-based dosing is required by a Medical Director as noted by **[verification required]**. All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation. In the approval indication for Roctavian, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Roctavian is recommended in those who meet the following criteria:

FDA-Approved Indication

67. Hemophilia A. Approve a one-time per lifetime dose if the patient meets the following (A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, R, S, T, U, V, W, X, Y, Z, AA, BB, and CC):

A) Patient is male*; AND

B) Patient is greater than or equal to 18 years of age; AND

C) Patient has severe hemophilia A as evidence by a baseline (without Factor VIII replacement therapy) Factor VIII level of < 1 IU/dL **[documentation required]**; AND

D) Patient does not have detectable pre-existing antibodies to adeno-associated virus 5 (AAV5) by an FDA-approved test **[documentation required]**; AND

E) Patient has a history of use of Factor VIII therapy for at least 150 exposure days; AND

F) Patient meets all of the following (i, ii, and iii):

- **i.** Factor VIII inhibitor titer testing has been performed within 30 days before intended receipt of Roctavian **[documentation required]**; AND
- **ii.** Patient does not currently have an inhibitor to Factor VIII **[documentation required]**; AND
- **iii.** Patient does not have a history of Factor VIII inhibitors **[documentation required]**; AND

G) Prophylactic therapy with Factor VIII will not be given after Roctavian administration once adequate Factor VIII levels have been achieved; AND

22. Note: Use of episodic Factor VIII therapy is acceptable for the treatment of bleeds and for surgery/procedures if needed as determined by the hemophilia specialist physician.

H) Patient has not received Roctavian in the past **[verification in claims history required]**; AND

23. Note: Verify through claims history that the patient has not previously received Roctavian AND, if no claim for Roctavian is present, the prescribing physician confirms that the patient has not previously received Roctavian.

I) Patient does not have a known hypersensitivity to mannitol; AND

J) Patient does not have an active acute or uncontrolled chronic infection; AND

K) Patient does not have chronic or active hepatitis B **[documentation required]**; AND

L) Patient does not have active hepatitis C **[documentation required]**; AND

M) Patient does not have evidence of significant hepatic fibrosis or cirrhosis; AND

N) Patient meets one of the following (i or ii):

i. Patient has undergone a liver health assessment within 30 days before intended receipt of Roctavian and meets all of the following (a, b, c, d, e, and f):

a) Alanine aminotransferase levels are ≤ 1.25 times the upper limit of normal **[documentation required]**; AND

b) Aspartate aminotransferase levels are ≤ 1.25 times the upper limit of normal **[documentation required]**; AND

c) Total bilirubin levels are ≤ 1.25 times the upper limit of normal **[documentation required]**; AND

d) Alkaline phosphatase levels are ≤ 1.25 times the upper limit of normal **[documentation required]**; AND

e) Gamma-glutamyl transferase levels are ≤ 1.25 times the upper limit of normal **[documentation required]**; AND

f) The International Normalized Ratio is < 1.4 **[documentation required]**; OR

ii. If the patient had one or more of the laboratory values listed in *Criteria a-f* above that was not at the value specified in *Criteria a-f* above, then a hepatologist has evaluated the patient and has determined that use of Roctavian is clinically appropriate **[documentation required]**; AND

O) Within 30 days before intended receipt of Roctavian, the platelet count was ≥ 100 x 10^9/L **[documentation required]**; AND

P) Within 30 days before intended receipt of Roctavian, the creatinine level was < 1.4 mg/dL **[documentation required]**; AND

Q) Patient has not used a systemic immunosuppressive agent within 30 days before intended receipt of Roctavian; AND

24. Note: Corticosteroids are not included as systemic immunosuppressive agents.

R) Patient does not have any disease or condition that would interfere with the compliance requirements that involve use of systemic corticosteroid therapy or systemic alternative immunosuppressive medications; AND

S) Patient does not have an immunosuppressive disorder; AND

T) Patient is not human immunodeficiency virus positive **[documentation required]**; AND

U) Patient does not have any additional bleeding disorder, besides hemophilia A; AND

V) Patient does not have a history of thrombosis or thrombophilia; AND

W) Patient does not have a current active malignancy; AND

25. Note: Current active malignancy does not include non-melanoma skin cancer.

X) Patient does not have a history of hepatic malignancy; AND

Y) Patient has not received a live vaccine within 30 days before intended receipt of Roctavian; AND

Z) The hemophilia specialist physician has discussed with the patient that for a period of up to 6 months after administration of Roctavian the following precautions should be taken (i and ii):

i. A male of reproductive potential (and his female partner) should prevent or postpone pregnancy by utilizing an effective form of contraception; AND

ii. A male should not donate semen; AND

AA) Medication is prescribed by a hemophilia specialist physician; AND

BB) Current patient body weight has been obtained within 30 days before intended receipt of Roctavian **[documentation required]**; AND

CC) If criteria A through BB are met, approve one dose of Roctavian to provide a one time (per lifetime) dose of 6 x 10^{13} vector genomes per kg by intravenous infusion **[verification required]**. Note: Roctavian is supplied in a carton (NDC 68135-927-48) that contains one single dose vial (NDC 68135-927-01) with an extractable volume of not less than 8 mL, containing 16 x 10^{13} vector genomes.

***** Refer to the Policy Statement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Roctavian is not recommended in the following situations:

123. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Hemophilia – Hemlibra Prior Authorization Policy
- Hemlibra® (emicizumab-kxwh subcutaneous injection – Genentech/Roche/Chugai)

REVIEW DATE: 05/24/2023

OVERVIEW

Hemlibra, a bispecific Factor IXa- and Factor X-directed antibody, is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with **hemophilia A** (congenital factor VIII deficiency) with or without factor VIII inhibitors.[1]

Hemlibra is recommended to be given as a loading dose by subcutaneous injection once weekly for the first 4 weeks, followed by a maintenance dose given either once weekly, once every 2 weeks, or once every 4 weeks.[1] Discontinue prophylactic use of bypassing medications the day before starting Hemlibra. The prophylactic use of Factor VIII products may be continued during the first week of Hemlibra prophylaxis. If appropriate, a patient or caregiver may self-inject Hemlibra. Self-administration is not recommended for children < 7 years of age.

Disease Overview

Hemophilia A is an X-linked bleeding disorder primarily impacting males caused by a deficiency in Factor VIII.[2-5] In the US, the incidence of hemophilia A in males is 1:5,000 with an estimated 20,000 people in the US living with hemophilia A. The condition is characterized by bleeding in joints, either spontaneously or in a provoked joint by trauma. Bleeding can occur in many different body areas as well (e.g., muscles, central nervous system). The bleeding manifestations can lead to substantial morbidity such as hemophilic arthropathy. Disease severity is usually defined by the plasma levels or activity of Factor VIII classified as follows: severe (levels < 1% of normal), moderate (levels 1% to 5% of normal), and mild (levels > 5% to < 40% of normal); phenotypic expression may vary. Approximately 50% of patients with hemophilia A are categorized as having severe disease.

Guidelines

Various guidelines discuss Hemlibra.[6-8]

- **National Hemophilia Foundation (NHF):** Two documents from the NHF Medical and Scientific Advisory Council (MASAC) provide recommendations regarding Hemlibra.[6,7] In general, Hemlibra has been shown to prevent or reduce the occurrence of bleeding in patients with hemophilia A in adults, adolescents, children and infants, both with and without inhibitors.[6] Factor VIII prophylaxis continuation during the week after initiation of Hemlibra is a reasonable approach.[7] However, because Hemlibra steady-state levels are not achieved until after four weekly doses, it may be reasonable to continue Factor VIII prophylaxis in selected patients based on bleeding history, as well as physical history, until they are ready to initiate maintenance dosing. Factor VIII products may be used for breakthrough bleeding events. Data are limited regarding the use of Hemlibra prophylaxis during immune tolerance induction.
- **World Federation of Hemophilia (WFH):** Guidelines from the WFH regarding hemophilia (2020) feature Hemlibra in a variety of clinical scenarios.[8] It is noted that the subcutaneous administration permits patients to initiate prophylaxis at a very young age. Other key benefits include its long half-life, high efficacy in bleed prevention, and reduction in bleeding episodes in patients with or without inhibitors.

Safety

Hemlibra has a Boxed Warning regarding thrombotic microangiopathy and thromboembolism.[1] Cases of thrombotic microangiopathy and thrombotic events were reported when on average a cumulative amount of > 100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) was given for 24 hours or more to patients receiving Hemlibra prophylaxis. Monitor for the development of thrombotic microangiopathy and thrombotic events when aPCC is given. Discontinue prophylactic use of bypassing agents the day before starting Hemlibra.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Hemlibra. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Hemlibra is recommended in those who meet one of the following criteria:

FDA-Approved Indications

38. Hemophilia A with Factor VIII Inhibitors. Approve for 1 year if the patient meets one the following (A or B):

N) Initial Therapy. Approve if the patient meets the following criteria (i, ii, iii, iv, v, and vi):

- **i.** Patient is using Hemlibra for routine prophylaxis to prevent or reduce the frequency of bleeding episodes; AND
- **ii.** Patient meets one of the following (a or b):
  - **a)** Patient has had a positive Factor VIII inhibitor titer greater than 5 Bethesda Units; OR
  - **b)** Patient has had a positive Factor VIII inhibitor titer less than or equal to 5 Bethesda Units and meets one of the following [(1) or (2)]:
    - **(1)** Patient has had an anamnestic response (current or past) to Factor VIII product dosing; OR
    - **(2)** Patient experienced an inadequate clinical response (current or past) to increased Factor VIII product dosing; AND
- **iii.** Prescriber attests that the patient will not be undergoing immune tolerance induction therapy while receiving Hemlibra; AND
- **iv.** Prescriber attests the following regarding use of bypassing agents (a and b):
  - **a)** If the patient is currently receiving a bypassing agent for prophylaxis, the bypassing agent therapy will be discontinued the day prior to initiation of Hemlibra; AND
  - **b)** Prophylactic use of bypassing agents will not occur while using Hemlibra; AND
    Note: Use of bypassing agents for the treatment of breakthrough bleeding is permitted. Examples of bypassing agents include NovoSeven RT (coagulation Factor VIIa [recombinant] intravenous infusion), Sevenfact (Factor VIIa [recombinant]-jncw intravenous infusion), and FEIBA (anti-inhibitor coagulant complex intravenous infusion).
- **v.** Prescriber attests the following regarding Factor VIII products (a and b):
  - **a)** If the patient is currently receiving a Factor VIII product for prophylactic use, the Factor VIII product will be discontinued within the initial 4-week loading dose period with Hemlibra; AND
  - **b)** Prophylactic use of Factor VIII products will not occur while using Hemlibra; AND
    Note: Use of Factor VIII products for the treatment of breakthrough bleeding is permitted.
- **vi.** Medication is prescribed by or in consultation with a hemophilia specialist; OR

O) Patient is Currently Receiving Hemlibra. Approve if the patient meets the following criteria (i, ii, iii, iv, v, and vi)

i. Patient is using Hemlibra for routine prophylaxis to prevent or reduce the frequency of bleeding episodes; AND

ii. Prescriber attests that the patient will not be undergoing immune tolerance induction therapy while receiving Hemlibra; AND

iii. Prescriber attests that prophylactic use of bypassing agents will not occur while using Hemlibra; AND

Note: Use of bypassing agents for the treatment of breakthrough bleeding is permitted. Examples of bypassing agents include NovoSeven RT (coagulation Factor VIIa [recombinant] intravenous infusion), Sevenfact (Factor VIIa [recombinant]-jncw intravenous infusion), and FEIBA (anti-inhibitor coagulant complex intravenous infusion).

iv. Prescriber attests that prophylactic use of Factor VIII products will not occur while using Hemlibra; AND

Note: Use of Factor VIII products for the treatment of breakthrough bleeding is permitted.

v. Medication is prescribed by or in consultation with a hemophilia specialist; AND

vi. Patient experienced a beneficial response to therapy according to the prescriber.

Note: Examples of a beneficial response to therapy include a reduction in bleeding events, in the severity of bleeding episodes, in the number of bleeding events that required treatment, and/or in the number of spontaneous bleeding events.

39. Hemophilia A without Factor VIII Inhibitors. Approve for 1 year if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve if the patient meets the following criteria (i, ii, iii, iv, and v):

i. Patient is using Hemlibra for routine prophylaxis to prevent or reduce the frequency of bleeding episodes; AND

ii. Patient meets one of the following criteria (a or b):

a) Patient has severe to moderate severe disease as defined by pretreatment Factor VIII levels ≤ 2% of normal; OR

b) Patient has moderate to mild disease as defined by pretreatment Factor VIII levels greater than 2% to less than 40% of normal and meets one of the following criteria [(1), (2), or (3)]:

(1) Patient has experienced a severe, traumatic, or spontaneous bleeding episode as determined by the prescriber; OR

Note: An example is a bleed involving the central nervous system.

(2) Patient has hemophilia-related joint damage, has experienced a joint bleed, or has a specific joint that is subject to recurrent bleeding (presence of a target joint); OR

(3) Patient is in a perioperative situation and/or has an additional clinical scenario regarding bleeding/bleeding risk in which the prescriber determines the use of Hemlibra is warranted.

Note: Examples include iliopsoas bleeding or severe epistaxis.

iii. Prescriber attests that prophylactic use of bypassing agent will not occur while using Hemlibra; AND

Note: Examples of bypassing agents include NovoSeven RT (coagulation Factor VIIa [recombinant] intravenous infusion), Sevenfact (Factor VIIa [recombinant]-jncw intravenous infusion), and FEIBA (anti-inhibitor coagulant complex intravenous infusion).

iv. Prescriber attests the following regarding Factor VIII products (a and b):

a) If receiving a Factor VIII product for prophylactic use, therapy will be discontinued within the initial 4-week loading dose period with Hemlibra; AND

b) Prophylactic use of Factor VIII products will not occur while using Hemlibra; AND

Note: Use of Factor VIII products for the treatment of breakthrough bleeding is permitted.

v. Medication is prescribed by or in consultation with a hemophilia specialist; OR

B) Patient is Currently Receiving Hemlibra. Approve if the patient meets the following criteria (i, ii, iii, iv, and v):

i. Patient is using Hemlibra for routine prophylaxis to prevent or reduce the frequency of bleeding episodes; AND

ii. Prescriber attests that prophylactic use of bypassing agent will not occur while using Hemlibra; AND

Note: Examples of bypassing agents include NovoSeven RT (coagulation Factor VIIa [recombinant] intravenous infusion), Sevenfact (Factor VIIa [recombinant]-jncw intravenous infusion), and FEIBA (anti-inhibitor coagulant complex intravenous infusion).

iii. Prescriber attests that prophylactic use of Factor VIII product will not occur while using Hemlibra; AND

Note: Use of Factor VIII products for the treatment of breakthrough bleeding is permitted.

iv. Medication is prescribed by or in consultation with a hemophilia specialist; AND

v. Patient experienced a beneficial response to therapy according to the prescriber.

Note: Examples of a beneficial response include a reduction in bleeding events, in the severity of bleeding episodes, in the number of bleeding events that required treatment, and/or in the number of spontaneous bleeding events.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Hemlibra is not recommended in the following situations:

25. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Hepatitis C – Epclusa Prior Authorization Policy
- Epclusa® (sofosbuvir/velpatasvir tablets and oral pellets – Gilead)
- sofosbuvir/velpatasvir tablets (authorized generic to Epclusa – Gilead)

REVIEW DATE: 04/05/2023

OVERVIEW

The fixed-dose combination of sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor, is indicated for the treatment of **chronic HCV genotype 1 through 6** infection in patients ≥ 3 years of age.[1] In patients with decompensated cirrhosis (Child-Pugh B or C), sofosbuvir/velpatasvir is administered with weight-based ribavirin. The FDA-approved duration of therapy with sofosbuvir/velpatasvir is 12 weeks for all patients.

Guidelines

The American Association for the Study of Liver Diseases/Infectious Diseases Society of America (AASLD/IDSA) provide recommendations for testing, monitoring, and treating HCV (October 24, 2022).[2] Instances in which the guidelines provide recommendations for sofosbuvir/velpatasvir outside of the FDA-approved indications are outlined below.

With the availability of pangenotypic HCV treatment regimens, HCV genotyping is no longer required prior to treatment initiation for all individuals. Pretreatment genotyping is still recommended in patients with cirrhosis and/or past unsuccessful HCV treatment, because treatment regimens may differ by genotype. However, for treatment-naïve patients without cirrhosis, although genotyping may impact the preferred treatment approach, it is not required if a pangenotypic regimen is used. The recommendations provide a simplified treatment algorithm for treatment-naïve adults where genotyping is not required.[2] Treatment-naïve adults without cirrhosis are eligible for simplified treatment if they do not have hepatitis B virus (not hepatitis B serum antigen [HBsAg] positive), are not pregnant, do not have hepatocellular carcinoma, and have not had a liver transplantation. In treatment-naïve adults without cirrhosis, the recommended regimens are Mavyret® (glecaprevir/pibrentasvir tablets) for 8 weeks or sofosbuvir/velpatasvir for 12 weeks.

In patients with decompensated cirrhosis, the guidelines offer a recommendation for patients who are ribavirin-ineligible to treat with sofosbuvir/velpatasvir for 24 weeks.[2] (Note: sofosbuvir/velpatasvir is FDA-approved in this setting in combination with ribavirin for 12 weeks for adult and pediatric patients). In pediatric patients with any genotype, sofosbuvir/velpatasvir with weight-based ribavirin is recommended in patients with prior exposure to an interferon-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors, with decompensated cirrhosis.

Although Vosevi® (sofosbuvir/velpatasvir/voxilaprevir tablets) is recommended in most instances for adults with no cirrhosis or compensated cirrhosis who have failed treatment with a sofosbuvir-containing regimen, sofosbuvir/velpatasvir is recommended in adults (genotypes 1 through 6) with decompensated cirrhosis who have failed therapy with a sofosbuvir-containing regimen. In this setting, sofosbuvir/velpatasvir is recommended for 24 weeks in combination with ribavirin. Data are limited to one Phase II study where sofosbuvir/velpatasvir was studied in patients with genotype 1, 2, and 3 who did not respond to velpatasvir-containing regimens including sofosbuvir/velpatasvir and Vosevi.[2,6] Retreatment with sofosbuvir/velpatasvir + ribavirin for 24 weeks yielded high overall response rates (sustained virologic response 12 weeks post-treatment [SVR12] 91% [n = 63/69]). Among patients with genotype 1 chronic

HCV, 97% of patients (n = 36/37) achieved SVR12. In patients with genotype 2 chronic HCV, SVR12 was attained in 95% of patients (n = 13/14) and in patients with genotype 3 chronic HCV, SVR12 was attained in 78% of patients (n = 14/18). Baseline NS5A resistance associated substitutions did not appear to impact SVR rates. No breakdown of the proportion of patients with decompensated cirrhosis was provided in the study.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of sofosbuvir/velpatasvir. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with sofosbuvir/velpatasvir as well as the monitoring required for adverse events and efficacy, approval requires sofosbuvir/velpatasvir to be prescribed by or in consultation with a with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of sofosbuvir/velpatasvir is recommended in those who meet one of the following criteria:

FDA-Approved Indications

68. Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 3, 4, 5, or 6, No Cirrhosis or Compensated Cirrhosis (Child-Pugh A). Approve for 12 weeks if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 3 years of age; AND
- **B)** Patient meets ONE of the following conditions (i or ii):
  - **i.** Patient does not have cirrhosis; OR
  - **ii.** Patient has compensated cirrhosis (Child-Pugh A); AND
- **C)** Patient has not been previously treated with sofosbuvir/velpatasvir; AND
- **D)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

2. Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 3, 4, 5, or 6, Decompensated Cirrhosis (Child-Pugh B or C), Adult. Approve for the duration below if the patient meets all of the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has decompensated cirrhosis (Child-Pugh B or C); AND
- **C)** Patient meets ONE of the following conditions (i or ii):
  - **i.** Patient is ribavirin-eligible, according to the prescriber: Approve for 12 weeks, if the medication is prescribed in combination with ribavirin; OR
  - **ii.** Patient is ribavirin-ineligible, according to the prescriber: Approve for 24 weeks; AND
- **D)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

3. Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 3, 4, 5, or 6, Decompensated Cirrhosis (Child-Pugh B or C), Pediatric Patient. Approve for 12 weeks if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 3 years of age and < 18 years of age; AND

B) Patient has decompensated cirrhosis (Child-Pugh B or C); AND
C) The medication will be prescribed in combination with ribavirin; AND
D) The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

Other Uses with Supportive Evidence

4. **Chronic Hepatitis C Virus (HCV), Genotype Unknown/Undetermined.** Approve for 12 weeks if the patient meets the following criteria (A, B, C, D, E, F, G, and H):
   A) Patient is ≥ 18 years of age; AND
   B) Patient does not have cirrhosis; AND
   C) Patient has not previously been treated for hepatitis C virus; AND
   D) Patient does not have hepatitis B virus; AND
   E) Patient is not pregnant; AND
   F) Patient does not have hepatocellular carcinoma; AND
   G) Patient has not had a liver transplantation; AND
   H) The medication will be prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

5. **Chronic Hepatitis C Virus (HCV), Genotype 1, 2, 3, 4, 5, or 6, Decompensated Cirrhosis (Child-Pugh B or C), Prior Null Responder, Prior Partial Responder, and Prior Relapser to sofosbuvir/velpatasvir or Vosevi**. Approve for 24 weeks if the patient meets the following criteria (A, B, C, D, and E):
   A) Patient is ≥ 3 years of age; AND
   B) Patient has decompensated cirrhosis (Child-Pugh B or C); AND
   C) Patient meets ONE of the following conditions (i or ii):
      i. Patient has been previously treated with sofosbuvir/velpatasvir; OR
      ii. Patient has previously been treated with Vosevi; AND
   D) The medication will be prescribed in combination with ribavirin; AND
   E) The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

6. **Patient Has Been Started on sofosbuvir/velpatasvir.** Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications or Other Uses with Supportive Evidence). Approve the duration described above to complete a course therapy (e.g., a patient who should receive 12 weeks, and has received 3 weeks, should be approved for 9 weeks to complete their 12-week course).

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of sofosbuvir/velpatasvir is not recommended in the following situations:

124. **Hepatitis C Virus (HCV) [any genotype], Combination with Any Other Direct-Acting Antivirals (DAAs) [Not Including Ribavirin].** Sofosbuvir/velpatasvir provides a complete antiviral regimen. Sofosbuvir/velpatasvir is not recommended to be used with other products containing sofosbuvir.
125. **Life Expectancy Less Than 12 Months Due to Non-Liver Related Comorbidities.** Patients with a limited life expectancy that cannot be remediated by HCV treatment, liver transplantation, or another directed therapy do not require antiviral treatment.[2] Patients with a short life expectancy owing to liver disease should be managed in consultation with an expert. Little evidence exists to support initiation

of HCV treatment in patients with a limited life expectancy (< 12 months) owing to non-liver-related comorbid conditions. For these patients, the benefits of HCV treatment are unlikely to be realized and palliative care strategies should take precedence.

126. Pediatric Patient (< 3 Years of Age). The safety and efficacy of sofosbuvir/velpatasvir have not been established in pediatric patients < 3 years of age.[1]

127. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

131. Epclusa® tablets and oral pellets [prescribing information]. Foster City, CA: Gilead; April 2022.
2. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. Testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org. Updated October 24, 2022. Accessed on March 24, 2023.
3. Gane EJ, Shiffman ML, Etzkorn K, et al. Sofosbuvir-velpatasvir with ribavirin for 24 weeks in HCV patients previously treated with a direct-acting antiviral regimen. *Hepatology*. 2017;66(4):1083-1089.

PRIOR AUTHORIZATION POLICY

POLICY: Hepatitis C – Harvoni Prior Authorization Policy
- Harvoni® (ledipasvir/sofosbuvir tablets and oral pellets – Gilead)
- ledipasvir/sofosbuvir tablets (authorized generics to Harvoni 90 mg/400 mg tablets only – Asegua)

REVIEW DATE: 09/13/2023

OVERVIEW

Ledipasvir/sofosbuvir is a fixed-dose combination of ledipasvir, a hepatitis C virus (HCV) NS5A inhibitor, and sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor. It is indicated for the treatment of **chronic HCV** infection in patients ≥ 3 years of age in the following instances:[1]
- Genotype 1, 4, 5, or 6 infection with or without compensated cirrhosis; and
- Genotype 1 infection with decompensated cirrhosis in combination with ribavirin; and
- Genotype 1 or 4 infection who are liver transplant recipients with or without compensated cirrhosis, in combination with ribavirin.

Dosing

In adults, the recommended dosage of ledipasvir/sofosbuvir is one tablet taken orally once daily with or without food.[1] The recommended dose of ledipasvir/sofosbuvir tablets or pellets in pediatric patients ≥ 3 years of age is based on weight. The ledipasvir/sofosbuvir pellets can be taken in pediatric patients who cannot swallow the tablet formulation. Table 1 below provides the recommended duration of therapy with ledipasvir/sofosbuvir. The ledipasvir/sofosbuvir authorized generic is only available as the 90 mg/400 mg strength tablet; ledipasvir/sofosbuvir is additionally available as a lower strength tablet (45 mg/200 mg) as well as oral pellets (45 mg/200 mg and 33.75 mg/150 mg).

Table 1. Recommended Treatment Duration for ledipasvir/sofosbuvir in Patients ≥ 3 Years of Age with Chronic HCV Genotype 1, 4, 5, or 6.[1]

Hepatitis C virus – Hepatitis C virus; * Harvoni for 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pretreatment HCV RNA < 6 million IU/mL; ** Treatment-experienced patients who have failed treatment with either peginterferon alfa + ribavirin or a hepatitis C virus protease inhibitor + peginterferon + ribavirin; † Harvoni for 12 weeks can be considered in treatment-experienced patients with cirrhosis who are eligible for ribavirin. The daily dose of ribavirin is weight-based (1,000 mg for patients < 75 kg and 1,200 mg for those ≥ 75 kg) administered in two divided doses. ‡ In patients with decompensated cirrhosis, the starting dosage of ribavirin is 600 mg and can be titrated up to 1,000 mg for patients <75 kg and 1,200 mg for those ≥75 kg in two divided doses with food. If the starting dosage of ribavirin is not well tolerated, the dosage should be reduced as clinically indicated based on hemoglobin levels. § The daily dosage of ribavirin is weight-based (1,000 mg for patients < 75 kg and 1,200 mg for those ≥ 75 kg) administered orally in two divided doses with food.

Guidelines

The American Association for the Study of Liver Diseases/Infectious Diseases Society of America have simplified recommendations for the management of chronic HCV in adults (October 24, 2022).[2] In treatment-naïve adults without cirrhosis, the recommended regimens are Mavyret® (glecaprevir/pibrentasvir tablets and oral pellets) for 8 weeks or Epclusa® (sofosbuvir/velpatasvir tablets [generics] and oral pellets) for 12 weeks. In treatment-naïve adults with compensated cirrhosis, the recommended regimens are Mavyret for 8 weeks (genotypes 1 through 6) or sofosbuvir/velpatasvir for 12 weeks (genotypes 1, 2, 4, 5, or 6; patients with genotype 3 require baseline NS5A resistance-associated substitution testing and those without Y93H can be treated with 12 weeks of Epclusa). Additional genotype-specific and/or special circumstance-specific recommendations are also provided for patients falling outside of these parameters. For the most up-to-date information always refer to the guidelines.

Ledipasvir/sofosbuvir continues to be recommended in various situations as outlined below in Table 2.

Table 2. AASLD Recommendations for Harvoni.[2]

Table 2 (continued). AASLD Recommendations for Harvoni.[2]
AASLD – American Association for the Study of Liver Diseases; DAA – Direct-acting antiviral; Y – Yes; N – No; HCV – Hepatitis C virus; HIV – Human immunodeficiency virus.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of ledipasvir/sofosbuvir. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with ledipasvir/sofosbuvir as well as the monitoring required for adverse events and long-term efficacy, approval requires ledipasvir/sofosbuvir to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of ledipasvir/sofosbuvir is recommended in those who meet one of the following criteria:

FDA-Approved Indications

69. Chronic Hepatitis C Virus (HCV), Genotype 1. Approve for the duration noted if the patient meets all of the following (A, B, and C):
- **A)** Patient is ≥ 3 years of age; AND
- **B)** Patient meets ONE of the following (i, ii or iii):
  - **i.** Approve for 8 weeks if the patient meets all of the following (a, b, c, d, and e):
    - **a)** Patient is treatment-naïve; AND
    - **b)** Patient does not have cirrhosis; AND
    - **c)** Patient does not have human immunodeficiency virus (HIV); AND
      Note: Patients with HIV should be reviewed using the same criteria as patients without HIV, using *Criteria ii or iii below*.
    - **d)** Patient is not awaiting liver transplantation; AND
      Note: Patients awaiting liver transplantation should be reviewed using *Criteria ii or iii below*
    - **e)** Baseline HCV RNA is < 6 million IU/mL; OR
  - **ii.** Approve for 12 weeks if the patient meets ONE the following (a, b, or c):
    - **a)** Patient is treatment-naïve AND does not meet criterion *Bi* above; OR
      Note: Treatment-naïve includes patients with or without HIV who are treatment-naïve with compensated [Child-Pugh A] cirrhosis regardless of baseline HCV RNA, or treatment-naïve patients with or without HIV without cirrhosis and baseline HCV RNA ≥ 6 million IU/mL. This would also include treatment-naïve patients awaiting transplant with compensated [Child-Pugh A] cirrhosis regardless of baseline HCV RNA or treatment-naïve patients awaiting transplant without cirrhosis and baseline HCV RNA ≥ 6 million IU/mL).
    - **b)** Patient has previously been treated for HCV and does not have cirrhosis; OR
      Note: For patients with compensated cirrhosis [Child-Pugh A] see criterion *Biii* below, for patients with decompensated cirrhosis [Child-Pugh B or C] see criterion *Biic* below.
    - **c)** Patient is treatment-naïve or has previously been treated for HCV and meets all of the following ([1], [2], and [3]):
      (1) Patient has decompensated (Child-Pugh B or C) cirrhosis; AND
      (2) Patient is ribavirin eligible; AND

Note: For ribavirin ineligible patients with decompensated cirrhosis, see criterion *Biiib* below

(3) The medication will be prescribed in combination with ribavirin; OR

iii. Approve for 24 weeks in patients who meet ONE of the following (a or b):

(1) Patient has previously been treated for HCV and has compensated (Child-Pugh A) cirrhosis; OR

(2) Patient is treatment-naïve or has previously been treated for HCV and the patient meets both of the following [1] and [2]):

a. Patient has decompensated cirrhosis (Child-Pugh B or C); AND

b. Patient is ribavirin ineligible, according to the prescriber; AND

C) The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

2. **Chronic Hepatitis C Virus (HCV), Genotype 4, 5, OR 6.** Approve for 12 weeks if the patient meets the following (A and B):
   A) Patient is ≥ 3 years of age; AND
   B) The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

3. **Recurrent Hepatitis C Virus (HCV) Post-Liver Transplantation, Genotypes 1 OR 4.** Approve for 12 weeks if the patient meets the following (A, B, C and D):
   A) Patient is ≥ 3 years of age; AND
   B) Patient has recurrent HCV after a liver transplantation; AND
   C) The medication will be prescribed in combination with ribavirin; AND
   D) The medication is prescribed by or in consultation with one of the following prescribers who is affiliated with a transplant center: a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

Other Uses with Supportive Evidence

4. **Recurrent Hepatitis C Virus (HCV) Post-Liver Transplantation, Genotypes 5 OR 6**. Approve for 12 weeks if the patient meets the following (A, B, C and D):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has recurrent HCV after a liver transplantation; AND
   C) The medication will be prescribed in combination with ribavirin; AND
   D) The medication is prescribed by or in consultation with one of the following prescribers who is affiliated with a transplant center: a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

5. **Hepatitis C Virus (HCV) Kidney Transplant Recipients, Genotype 1 or 4.** Approve for 12 weeks if the patient meets the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient is a kidney transplant recipient with HCV; AND
   C) The medication is prescribed by or in consultation with one of the following prescribers who is affiliated with a transplant center: a gastroenterologist, hepatologist, infectious diseases physician, nephrologist, liver transplant physician, or a renal transplant physician.

6. **Patient Has Been Started on ledipasvir/sofosbuvir.** Approve ledipasvir/sofosbuvir for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications or Other Uses with Supportive Evidence). Approve for the duration described

above to complete a course of therapy (e.g., a patient who should receive 12 weeks, and has received 3 weeks should be approved for 9 weeks to complete their 12-week course).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of ledipasvir/sofosbuvir is not recommended in the following situations:

128. Hepatitis C Virus (HCV) [any genotype], Combination with Any Other Direct-Acting Antivirals (DAAs) Not Including Ribavirin. Ledipasvir/sofosbuvir provides a complete antiviral regimen for patients with genotype 1 HCV. Ledipasvir/sofosbuvir is not recommended to be used with other products containing sofosbuvir.

129. Life Expectancy Less Than 12 Months Due to Non-Liver Related Comorbidities. Patients with limited life expectancy for whom HCV therapy would not improve symptoms or prognosis do not require treatment.[2] According to AASLD guidance, the panel recommends treatment for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. For these patients, the benefits of HCV treatment are unlikely to be realized, and palliative care strategies should take precedence.

130. Pediatric Patients (Age < 3 years). The safety and efficacy of ledipasvir/sofosbuvir have not been established in pediatric patients < 3 years of age.[1]

131. Retreatment with ledipasvir/sofosbuvir in Patients Who Have Previously Received ledipasvir/sofosbuvir (e.g., retreatment in prior null responders, prior partial responders, prior relapse patients, patients who have not completed a course of therapy due to an adverse reaction or for other reasons). There are other direct-acting antivirals indicated for patients who have previously been treated with ledipasvir/sofosbuvir.

132. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

132. Harvoni® tablets and oral pellets [prescribing information]. Foster City, CA: Gilead; March 2020.
2. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. Testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org. Updated October 24, 2022. Accessed on August 17, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Hepatitis C – Mavyret Prior Authorization Policy
- Mavyret® (glecaprevir/pibrentasvir tablets and oral pellets – AbbVie)

REVIEW DATE: 04/05/2023

OVERVIEW

Mavyret, a direct-acting antiviral, contains glecaprevir, a pangenotypic NS3/4A protease inhibitor and pibrentasvir, a pangenotypic NS5A inhibitor.[1] It is indicated for the treatment of **chronic hepatitis C virus** (HCV) in the following scenarios:

- Patients ≥ 3 years of age with genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A).
- Patients ≥ 3 years of age with genotype 1 infection who have previously been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both.

Dosing

The duration of therapy is based on prior treatment experience, genotype, and the presence or absence of cirrhosis (see Tables 1 and 2). In addition, Mavyret is recommended for 12 weeks in patients ≥ 3 years of age who are liver or kidney transplant recipients. Similar to non-transplant recipients, a 16-week treatment duration is recommended in genotype 1-infected patients who are NS5A inhibitor-experienced without prior treatment with an NS3/4A protease inhibitor or in genotype 3-infected patients who are treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or Sovaldi® (sofosbuvir tablets/oral pellets).

Table 1. Recommended Duration for Treatment-Naïve Patients.[1]
HCV – Hepatitis C virus.

Table 2. Recommended Duration for Treatment-Experienced Patients.[1]
HCV – Hepatitis C virus; PRS – Prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or Sovaldi® (sofosbuvir tablets), but no prior treatment experience with an HCV NS3/4A protease inhibitor (PI) or NS5A inhibitor; PI – Protease inhibitor; [1] Regimens containing Olysio® (simeprevir capsules) and Sovaldi, or Olysio, Victrelis® (boceprevir capsules), or Incivek® (telaprevir tablets) with interferon or pegylated interferon and ribavirin were studied; [2] Regimens containing ledipasvir/sofosbuvir or Daklinza® (daclatasvir tablets) + pegylated interferon + ribavirin [unapproved regimen] were studied.

Guidelines

The American Association for the Study of Liver Diseases/Infectious Diseases Society of America (AASLD/IDSA) provide recommendations for testing, monitoring, and treating HCV (October 24, 2022).[2] Instances in which the guidelines provide recommendations for Mavyret outside of the FDA-approved indications are outlined below.

With the availability of pangenotypic HCV treatment regimens, HCV genotyping is no longer required prior to treatment initiation for all individuals. Pretreatment genotyping is still recommended in patients with cirrhosis and/or past unsuccessful HCV treatment, because treatment regimens may differ by genotype. However, for treatment-naïve patients without cirrhosis, although genotyping may impact the preferred treatment approach, it is not required if a pangenotypic regimen is used. Treatment-naïve adults without cirrhosis are eligible for simplified treatment if they do not have hepatitis B virus (not hepatitis B serum antigen [HBsAg] positive), are not pregnant, do not have hepatocellular carcinoma, and have not had a liver transplantation. In treatment-naïve adults without cirrhosis, the recommended regimens are Mavyret for 8

weeks or sofosbuvir/velpatasvir for 12 weeks. Additional genotype-specific and/or special circumstance-specific recommendations are also provided for patients falling outside of these parameters.

Mavyret is recognized as a recommended regimen (12 weeks) for the treatment of patients with recurrent HCV post-liver transplantation (without cirrhosis or with compensated cirrhosis).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Mavyret. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Mavyret as well as the monitoring required for adverse events and efficacy, approval requires Mavyret to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mavyret is recommended in those who meet one of the following criteria:

FDA-Approved Indications

70. Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 3, 4, 5, or 6, Treatment-Naïve. Approve for 8 weeks if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 3 years of age; AND
- **B)** Patient is HCV treatment-naïve (the patient has not previously received treatment for their chronic HCV infection); AND
- **C)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

71. Chronic Hepatitis C Virus (HCV), Genotype 1, Treatment-Experienced. Approve for the duration noted if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 3 years of age; AND
- **B)** Patient meets ONE of the following conditions (i, ii, iii, or iv):
  - **i.** NS5A-Experienced, NS34-Naïve: Approve for 16 weeks if the patient meets the following criteria (a, b, and c):
    - **a)** Patient does not have cirrhosis or has compensated cirrhosis (Child-Pugh A); AND
    - **b)** Patient had a prior null response, prior partial response, or had relapse after prior treatment with one of the following NS5A-inhibitor containing products: Daklinza (daclatasvir tablets), sofosbuvir/velpatasvir, ledipasvir/sofosbuvir; AND
    - **c)** Patient has not previously been treated with one of the following NS3/4A inhibitor or NS3/4A inhibitor-containing products: Olysio (simeprevir capsules), Victrelis (boceprevir capsules), or Incivek (telaprevir tablets), Technivie (ombitasvir/paritaprevir/ritonavir tablets), Viekira Pak (ombitasvir/paritaprevir/ritonavir tablets; dasabuvir tablets, co-packaged), Viekira XR (dasabuvir/ombitasvir/paritaprevir/ritonavir extended-release tablets), Vosevi (sofosbuvir/velpatasvir/voxilaprevir tablets); or Zepatier (elbasvir/grazoprevir tablets); OR
  - **ii.** NS3/4-Experienced, NS5A-Naïve: Approve for 12 weeks if the patient meets the following criteria (a, b, and c):
    - **a)** Patient does not have cirrhosis or has compensated cirrhosis (Child-Pugh A); AND

b) Patient has not previously been treated with one of the following NS5A-inhibitor-containing products: Daklinza (daclatasvir tablets), sofosbuvir/velpatasvir, ledipasvir/sofosbuvir, Technivie (ombitasvir/paritaprevir/ritonavir tablets), Viekira Pak (ombitasvir/paritaprevir/ritonavir tablets; dasabuvir tablets, co-packaged), Viekira XR (dasabuvir/ombitasvir/paritaprevir/ritonavir extended-release tablets), Vosevi (sofosbuvir/velpatasvir/voxilaprevir tablets), or Zepatier (elbasvir/grazoprevir tablets); AND

c) Patient had a prior null response, prior partial response, or had relapse after prior treatment with one of the following NS3/4A inhibitor or NS3/4A inhibitor-containing products: Olysio (simeprevir capsules), Victrelis (boceprevir capsules), or Incivek (telaprevir tablets); OR

iii. Pegylated Interferon/Interferon, Ribavirin, Sovaldi-Experienced: Approve for 8 weeks if the patient meets both of the following criteria (a and b):

a) Patient does not have cirrhosis; AND

b) Patient had a prior null response, prior partial response, or had relapse after prior treatment with one of the following regimens: interferon ± ribavirin, pegylated interferon ± ribavirin, Sovaldi (sofosbuvir tablets/oral pellets) + ribavirin, Sovaldi + pegylated interferon + ribavirin; OR

iv. Pegylated Interferon/Interferon, Ribavirin, Sovaldi-Experienced: Approve for 12 weeks if the patient meets both of the following criteria (a and b):

a) Patient has compensated cirrhosis (Child-Pugh A); AND

b) Patient had a prior null response, prior partial response, or had relapse after prior treatment with one of the following regimens: interferon ± ribavirin, pegylated interferon ± ribavirin, Sovaldi (sofosbuvir tablets/oral pellets) + ribavirin, Sovaldi + pegylated interferon + ribavirin; AND

C) The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

72. **Chronic Hepatitis C Virus (HCV), Genotype 2, 4, 5, or 6, Treatment-Experienced**. Approve for the duration noted if the patient meets the following criteria (A, B, and C):
    A) Patient is ≥ 3 years of age ; AND
    B) Patient meets ONE of the following (i or ii):
        i. Approve for 8 weeks if the patient meets both of the following criteria (a and b):
            a) Patient does not have cirrhosis; AND
            b) Patient had a prior null response, prior partial response, or had relapse after prior treatment with one of the following regimens: interferon ± ribavirin, pegylated interferon ± ribavirin, Sovaldi (sofosbuvir tablets/oral pellets)+ ribavirin, Sovaldi + pegylated interferon + ribavirin; OR
        ii. Approve for 12 weeks if the patient meets both of the following criteria (a and b):
            a) Patient has compensated cirrhosis (Child-Pugh A); AND
            b) Patient had a prior null response, prior partial response, or had relapse after prior treatment with one of the following regimens: interferon ± ribavirin, pegylated interferon ± ribavirin, Sovaldi (sofosbuvir tablets/oral pellets) + ribavirin, Sovaldi + pegylated interferon + ribavirin; AND
    C) The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

73. **Chronic Hepatitis C Virus (HCV), Genotype 3, Treatment-Experienced**. Approve for 16 weeks if the patient meets the following criteria (A, B, C, and D):
    A) Patient is ≥ 3 years of age; AND
    B) Patient does not have cirrhosis or has compensated cirrhosis (Child-Pugh A); AND
    C) Patient had a prior null response, prior partial response, or had relapse after prior treatment with one of the following regimens: interferon ± ribavirin, pegylated interferon ± ribavirin, Sovaldi (sofosbuvir tablets/oral pellets) + ribavirin, Sovaldi + pegylated interferon + ribavirin; AND
    D) The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

74. **Hepatitis C Virus (HCV) Kidney or Liver Transplant Recipient, Genotype 1, 2, 3, 4, 5, or 6**. Approve for the duration noted if the patient meets all of the following criteria (A, B, C, and D):
    A) Patient is ≥ 3 years of age; AND
    B) Patient is a kidney or liver transplant recipient with HCV; AND
    C) Patient meets ONE of the following conditions (i, ii, or iii):
        i. Patient has genotype 2, 4, 5, or 6 HCV: Approve for 12 weeks; OR
        ii. Patient has genotype 1 HCV: Approve for the duration below (a or b):
            a) NS5A-Experienced, NS3/4-Naïve: Approve for 16 weeks if the patient meets both of the following criteria (1 and 2):
                (1) Patient had a prior null response, prior partial response, or had relapse after prior treatment with one of the following NS5A-inhibitor containing products: Daklinza (daclatasvir tablets), sofosbuvir/velpatasvir, ledipasvir/sofosbuvir; AND
                (2) Patient has not previously been treated with one of the following NS3/4A inhibitor or NS3/4A inhibitor-containing products: Olysio (simeprevir capsules), Victrelis (boceprevir capsules), or Incivek (telaprevir tablets), Technivie (ombitasvir/paritaprevir/ritonavir tablets), Viekira Pak (ombitasvir/paritaprevir/ritonavir tablets; dasabuvir tablets, co-packaged), Viekira XR (dasabuvir/ombitasvir/paritaprevir/ritonavir extended-release tablets), Vosevi (sofosbuvir/velpatasvir/voxilaprevir tablets); or Zepatier (elbasvir/grazoprevir tablets). OR
            b) Approve for 12 weeks for all other patients with genotype 1 HCV; OR

iii. Patient has genotype 3 HCV: Approve for the duration below (a or b):
- **a)** Approve for 16 weeks if the patient had a prior null response, prior partial response, or had relapse after prior treatment with one of the following regimens: interferon ± ribavirin, pegylated interferon ± ribavirin, Sovaldi (sofosbuvir tablets/oral pellets) + ribavirin, Sovaldi + pegylated interferon + ribavirin; OR
- **b)** Approve for 12 weeks for all other patients with genotype 3 HCV; AND

D) The medication is prescribed by or in consultation with one of the following prescribers who is affiliated with a transplant center: gastroenterologist, hepatologist, infectious diseases physician, nephrologist, renal transplant physician, or liver transplant physician.

Other Uses with Supportive Evidence

75. Chronic Hepatitis C Virus (HCV), Genotype Unknown/Undetermined. Approve for 8 weeks if the patient meets the following criteria (A, B, C, D, E, F, G, and H):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient does not have cirrhosis; AND
- **C)** Patient has not previously been treated for hepatitis C virus; AND
- **D)** Patient does not have hepatitis B virus; AND
- **E)** Patient is not pregnant; AND
- **F)** Patient does not have hepatocellular carcinoma; AND
- **G)** Patient has not had a liver transplantation; AND
- **H)** The medication will be prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

76. Recurrent Hepatitis C Virus (HCV) Post-Liver Transplantation, Genotype 1, 2, 3, 4, 5, or 6. Approve for 12 weeks if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 3 years of age; AND
- **B)** Patient has recurrent HCV after a liver transplantation; AND
- **C)** The medication is prescribed by or in consultation with one of the following prescribers who is affiliated with a transplant center: a gastroenterologist, hepatologist, infectious diseases physician, or liver transplant physician.

77. Patient Has Been Started on Mavyret. Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications or Other Uses with Supportive Evidence). Approve the duration described above to complete a course therapy (e.g., a patient who should receive 12 weeks, and has received 3 weeks should be approved for 9 weeks to complete their 12-week course).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mavyret is not recommended in the following situations:

133. Hepatitis C Virus (HCV) Child-Pugh Class B or C Liver Disease (Moderate or Severe Hepatic Impairment). Mavyret is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C).

134. Hepatitis C Virus (HCV) [any genotype], Combination with Any Other Direct-Acting Antivirals. Mavyret provides a complete antiviral regimen.

135. Life Expectancy Less Than 12 Months Due to Non-Liver Related Comorbidities. Patients with a limited life expectancy that cannot be remediated by HCV treatment, liver transplantation, or another directed therapy do not require antiviral treatment.[2] Patients with a short life expectancy owing to liver disease should be managed in consultation with an expert. Little evidence exists to support initiation of HCV treatment in patients with a limited life expectancy (< 12 months) owing to non-liver-related comorbid conditions. For these patients, the benefits of HCV treatment are unlikely to be realized and palliative care strategies should take precedence.

136. Pediatric Patient (< 3 Years of Age). The safety and efficacy of Mavyret have not been established in pediatric patients < 3 years of age.[1]

137. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

464. Mavyret® tablets and oral pellets [prescribing information]. North Chicago, IL: AbbVie; September 2021.
465. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. Testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org. Updated October 24, 2022. Accessed on March 24, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Hepatitis C – Sovaldi Prior Authorization Policy
- Sovaldi® (sofosbuvir tablets and oral pellets – Gilead)

REVIEW DATE: 01/18/2023

OVERVIEW

Sovaldi, a hepatitis C virus (HCV) nucleotide analog non-serine (NS)5B polymerase inhibitor, is indicated for the following uses:[1]

- **Chronic HCV genotype 1, 2, 3 or 4 infection**, adults without cirrhosis or with compensated cirrhosis as a component of a combination antiviral treatment.
- **Chronic HCV genotype 2 or 3 infection**, pediatric patients ≥ 3 years of age without cirrhosis or with compensated cirrhosis in combination with ribavirin.

The place in therapy for Sovaldi has greatly lessened or is non-existent in most cases due to the availability of other direct-acting antivirals (DAAs) with greater efficacy for many genotypes. Regimens with Sovaldi + peginterferon + ribavirin or Sovaldi + weight-based ribavirin are no longer recommended in treatment guidelines with the exception of pediatric patients due to inferior efficacy compared with other all-oral regimens for all genotypes. Table 1 provides pediatric recommendations.

Table 1. Sovaldi Treatment Regimen in Pediatric Patients (≥ 3 years of age).[1]

Guidelines

According to the American Association for the Study of Liver Diseases (AASLD) guidelines, weight-based Sovaldi + ribavirin for treatment-naive or interferon-experienced (± ribavirin) children aged ≥3 years with genotype 2 or 3, without cirrhosis or with compensated cirrhosis (Child-Pugh A) is no longer favored because pangenotypic ribavirin-free treatments are now available for children as young as 3 years of age.[2] The AASLD recommends Epclusa® (sofosbuvir/velpatasvir tablets and oral pellets) and Mavyret® (glecaprevir/pibrentasvir tablets and oral pellets) for the treatment of patients ≥ 3 years of age with genotypes 1 through 6 chronic HCV who are treatment-naïve or interferon-experienced, with or without compensated cirrhosis; Harvoni® (ledipasvir/sofosbuvir tablets and oral pellets) is also an option for children ≥ 3 years of age with genotypes 1, 4, 5, or 6 chronic HCV.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Sovaldi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sovaldi as well as the monitoring required for adverse events and efficacy, approval requires Sovaldi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sovaldi is recommended in those who meet one of the following criteria:

FDA-Approved Indications

40. Chronic Hepatitis C Virus (HCV) Genotype 2. Approve for 12 weeks if the patient meets the following criteria (A, B, C, and D):

A) Patient is ≥ 3 years of age and < 18 years of age; AND

B) Patient does not have decompensated cirrhosis (Child-Pugh B or C)

- Note: Coverage is provided for patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis; AND

C) The medication will be prescribed in combination with ribavirin; AND

D) The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

41. Chronic Hepatitis C Virus (HCV) Genotype 3. Approve for 24 weeks if the patient meets the following criteria (A, B, C, and D):

A) Patient is ≥ 3 years of age and < 18 years of age; AND

B) Patient does not have decompensated cirrhosis (Child-Pugh B or C)

- Note: Coverage is provided for patients without cirrhosis or for patients with compensated (Child-Pugh A) cirrhosis; AND

C) The medication will be prescribed in combination with ribavirin; AND

D) The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

Other Uses with Supportive Evidence

3. **Patient Has Been Started on Sovaldi.** Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications or Other Uses with Supportive Evidence). Approve the duration described above to complete a course therapy (e.g., a patient who should receive 12 weeks and has received 3 weeks should be approved for 9 weeks to complete their 12-week course).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sovaldi is not recommended in the following situations:

1. **HCV (Any Genotype), Combination Use with Direct-Acting Antivirals (DAAs) Other than Ribavirin.** In adults with any genotype chronic HCV with or without compensated cirrhosis who have failed treatment with Mavyret, retreatment with Mavyret + Sovaldi + ribavirin is a recommended regimen based on data from a Phase IIIb study evaluating the safety and efficacy of Mavyret + Sovaldi + weight-based ribavirin as a 12- or 16-week retreatment regimen for patients who experienced virologic failure to Mavyret within the context of a previous clinical trial. Non-cirrhotic Mavyret non-responders with genotype 1, 2, 4, 5, or 6 who were naïve to protease and NS5A inhibitors received 12 weeks Mavyret + Sovaldi and weight-based ribavirin. Patients with genotype 3, and/or compensated cirrhosis, and/or protease/NS5A experience (prior to their initial Mavyret treatment) received 16 weeks of therapy with the same regimen. In a preliminary analysis, 96% (n = 22/23) of these patients achieved SVR with a single relapse in a cirrhotic patient with genotype 1a. Vosevi is also a recommended regimen in this instance and it is FDA-approved for such use.
2. **Life Expectancy < 12 Months Due to Non-Liver Related Comorbidities.** According to AASLD guidance, little evidence exists to support initiation of HCV treatment in patients with limited life expectancy (< 12 months) due to non-liver-related comorbid conditions.[2] For these patients, the benefits of HCV treatment are unlikely to be realized, and palliative care strategies should take precedence.

3. **Monotherapy with Sovaldi.** Sovaldi is indicated as a component of a combination antiviral treatment regimen for HCV.[1]

4. **Pediatric Patients (Age < 3 years).** The safety and efficacy of Sovaldi have not been established in pediatric patients < 3 years of age.[1]

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

133. Sovaldi® tablets and oral pellets [prescribing information]. Foster City, CA: Gilead; March 2020.
2. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. Testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org. Updated October 24, 2022. Accessed on: January 6, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Hepatitis C – Vosevi Prior Authorization Policy
- Vosevi® (sofosbuvir/velpatasvir/voxilaprevir tablets – Gilead)

REVIEW DATE: 08/02/2023

OVERVIEW

Vosevi is a direct-acting-antiviral (DAA) containing sofosbuvir, a nucleotide analog NS5B polymerase inhibitor, velpatasvir, a hepatitis C virus (HCV) NS5A inhibitor, and voxilaprevir, a HCV NS3/4A protease inhibitor.[1] It is indicated for the treatment of adults with **chronic HCV** with or without compensated cirrhosis who have:

- **Genotype 1, 2, 3, 4, 5, or 6** infection and have **previously been treated with an HCV regimen containing an NS5A inhibitor**;
- **Genotype 1a or 3** infection and who have **previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor**.

Additional benefit of Vosevi over Epclusa® (sofosbuvir/velpatasvir tablets/oral granules) was not shown in adults with genotype 1b, 2, 4, 5, or 6 infection previously treated with sofosbuvir without an NS5A inhibitor.[1] The recommended dosage of Vosevi is one tablet, taken orally, once daily (QD) with food for 12 weeks.

Guidelines

For the most up-to-date guideline information always refer to the American Association for the Study of Liver Diseases (AASLD) guidelines.[3]

Vosevi is recommended in in several circumstances in adults, mainly in patients who are direct-acting antiviral-experienced. Some of these recommendations are based on very limited data and are not FDA-approved indications for Vosevi (e.g., retreatment with Vosevi in patients who have failed Vosevi in the past [one case report]).

- **Genotype 1 through 6 chronic HCV, ± compensated cirrhosis, treatment-experienced:**
  - Prior sofosbuvir-based treatment failure: Vosevi for 12 weeks; the addition of ribavirin is recommended in patients with genotype 3 HCV with compensated cirrhosis.
  - Prior Mavyret® (glecaprevir/pibrentasvir tablets and oral pellets) treatment failure: Vosevi for 12 weeks; the addition of ribavirin is recommended in patients with compensated cirrhosis.
  - Prior Zepatier® (elbasvir/grazoprevir tablets) treatment failure: Vosevi for 12 weeks; the addition of ribavirin is recommended in patients with compensated cirrhosis.
  - Prior Vosevi treatment failure: Vosevi + ribavirin for 24 weeks.
- **Kidney transplant, genotype 1 through 6 HCV, ± compensated cirrhosis, treatment-experienced:**
  - Prior direct-acting antiviral-failure: Vosevi ± ribavirin for 12 weeks; the addition of ribavirin should be considered for patients with compensated cirrhosis and multiple negative baseline characteristics.
- **Recurrent HCV post-liver transplantation, genotype 1 through 6 infection of the allograft, ± compensated cirrhosis, treatment-naïve:**

- Prior direct-acting antiviral failure: Vosevi for 12 weeks is recommended; the addition of ribavirin should be considered for patients with compensated cirrhosis and multiple negative baseline characteristics.

Vosevi for 12 weeks is an alternative recommendation for treatment-naïve adults with genotype 3 HCV with compensated cirrhosis who have the Y93H resistance-associated substitution.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vosevi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vosevi as well as the monitoring required for adverse events and efficacy, approval requires Vosevi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vosevi is recommended in those who meet one of the following criteria:

FDA-Approved Indications

78. Chronic Hepatitis C Virus (HCV) Genotype 1b, 2, 4, 5, or 6. Approve for 12 weeks if the patient meets the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following (i or ii):
  - **i.** Patient does not have cirrhosis; OR
  - **ii.** Patient has compensated cirrhosis (Child-Pugh A); AND
- **C)** Patient had a prior null response, prior partial response, or relapse after prior treatment with an HCV direct-acting antiviral regimen containing an NS5A inhibitor; AND
  Note: Examples of direct-acting antivirals that are, or contain, an NS5A inhibitor include: Daklinza (daclatasvir tablets), Epclusa (sofosbuvir/velpatasvir tablets/oral pellets), Harvoni (ledipasvir/sofosbuvir tablets/oral pellets), Mavyret (glecaprevir/pibrentasvir tablets/oral pellets), Viekira Pak (ombitasvir/paritaprevir/ritonavir tablets; dasabuvir tablets, co-packaged), Zepatier (elbasvir/grazoprevir tablets).
- **D)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

79. Chronic Hepatitis C Virus, Genotype 1a or 3. Approve for 12 weeks if the patient meets the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following (i or ii):
  - **i.** Patient does not have cirrhosis; OR
  - **ii.** Patient has compensated cirrhosis (Child-Pugh A); AND
- **C)** Patient meets ONE of the following (i or ii):
  - **i.** Patient had a prior null response, prior partial response, or relapse after prior treatment with an HCV direct-acting antiviral regimen containing an NS5A inhibitor; OR
    Note: Examples of direct-acting antivirals that are, or contain, an NS5A inhibitor include: Daklinza (daclatasvir tablets), Epclusa (sofosbuvir/velpatasvir tablets/oral pellets), Harvoni

(ledipasvir/sofosbuvir tablets/oral pellets), Mavyret (glecaprevir/pibrentasvir tablets/oral pellets), Viekira Pak (ombitasvir/paritaprevir/ritonavir tablets; dasabuvir tablets, co-packaged), Zepatier (elbasvir/grazoprevir tablets).

ii. Patient had a prior null response, prior partial response, or relapse after prior treatment with an HCV DAA regimen containing Sovaldi (sofosbuvir tablets/oral pellets) + a non-NS5A inhibitor; AND

Note: Examples of regimens that contain Sovaldi (sofosbuvir tablets/oral pellets) + a non-NS5A inhibitor include: Sovaldi + NS3 inhibitors (Olysio [simeprevir capsules], Victrelis [boceprevir capsules], or Incivek [telaprevir tablets]) or Sovaldi + ribavirin ± pegylated interferon.

D) The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

Other Uses with Supportive Evidence

80. Chronic Hepatitis C Virus (HCV) Genotype 1b, 2, 4, 5, or 6. Approve for 12 weeks if the patient meets the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient meets ONE of the following (i or ii):

i. Patient does not have cirrhosis; OR

ii. Patient has compensated cirrhosis (Child-Pugh A); AND

C) Patient had a prior null response, prior partial response, or relapse after prior treatment with an HCV DAA regimen containing Sovaldi (sofosbuvir tablets/oral pellets) + a non-NS5A inhibitor; AND

Note: Examples of regimens that contain Sovaldi (sofosbuvir tablets/oral pellets) + a non-NS5A inhibitor include: Sovaldi + NS3 inhibitors (Olysio [simeprevir capsules], Victrelis [boceprevir capsules], or Incivek [telaprevir tablets]) or Sovaldi + ribavirin ± pegylated interferon.

D) The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

81. Patient Has Been Started on Vosevi. Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications or Other Uses with Supportive Evidence). Approve the duration described above to complete a course therapy (e.g., a patient who should receive 12 weeks, and has received 3 weeks should be approved for 9 weeks to complete their 12-week course).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vosevi is not recommended in the following situations:

1. **Hepatitis C Virus (HCV) [any genotype], Combination with Any Other Direct-Acting Antivirals (DAAs).** Vosevi provides a complete antiviral regimen.

2. **Life Expectancy Less Than 12 Months Due to Non-Liver Related Comorbidities.** According to the AASLD guidelines, patients with a limited life expectancy that cannot be remediated by HCV treatment, liver transplantation, or another directed therapy do not require antiviral treatment.[3]

3. **Pediatric Patients (Age < 18 Years).** The safety and efficacy of Vosevi have not been established in pediatric patients < 18 years of age.[1]

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

134. Vosevi® tablets [prescribing information]. Foster City, CA: Gilead; November 2019.
135. Bourliere M, Gordon SC, Flamm SL, et al. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. *N Engl J Med*. 2017;376(22):214-2146.
3. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. Testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org. Updated October 24, 2022. Accessed on July 24, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Hepatitis C – Zepatier Prior Authorization Policy
- Zepatier® (grazoprevir/elbasvir tablets – Merck)

REVIEW DATE: 02/15/2023

OVERVIEW

Zepatier, an oral fixed-dose combination tablet containing grazoprevir, a second generation protease inhibitor and elbasvir, an NS5A inhibitor, is indicated with or without ribavirin for the treatment of genotypes 1 and 4 **chronic hepatitis C virus** (HCV) in adults and pediatric patients ≥ 12 years of age or weighing at least 30 kg.[1]

Safety

Zepatier is contraindicated in patients with Child-Pugh B or C liver disease (decompensated cirrhosis). Zepatier is also contraindicated with inhibitors of organic anion transporting polypeptides 1B1/3 that are known or expected to significantly increase grazoprevir plasma concentrations, strong inducers of cytochrome P450 3A, and efavirenz.

Dosing

The duration of treatment is outlined below (Table 1) and is dependent on the patient population. Prior to initiating Zepatier in patients with genotype 1a infection, testing for the NS5A resistance associated polymorphism is recommended to guide treatment duration. In patients with genotype 1a and this polymorphism present at baseline, 12 weeks of treatment with Zepatier resulted in lower rates of sustained viral response 12 weeks after treatment completion relative to patients with genotype 1a without the presence of this baseline polymorphism.

Table 1. Recommended Zepatier Dosage Regimens for the Treatment of Genotype 1 or 4 Chronic HCV.[1]

HCV – Hepatitis C virus; TN – Treatment naïve; PR – Pegylated interferon/ribavirin; [*] Patients who have failed treatment with PR; [†] NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93; [§] The optimal Zepatier-based treatment regimen and duration of therapy for PR + HCV protease inhibitor-experienced genotype 1a-infected patients with one or more baseline NS5A resistance-associated polymorphisms at positions 28, 30, 31, and 93 has not been established; PI – PI – Protease inhibitor; [β] Patients who have failed treatment with PR + and NS3/4A PI (i.e., Victrelis® [boceprevir capsules], Incivek® [telaprevir tablets], or Olysio® [simeprevir capsules]); TE – Treatment-experienced; NA – Not applicable.

Guidelines

According to the American Association for the Study of Liver Diseases (AASLD) [October 2022] NS5A RAS testing is recommended for genotype 1a-infected, treatment-naive or -experienced patients being considered for Zepatier.[2] If present, a different regimen should be considered. Zepatier is recognized as an alternative regimen in treatment-naïve patients with Genotype 1a with or without compensated cirrhosis, and a recommended treatment option in patients with genotype 1b or 4 chronic HCV with or without compensated cirrhosis in guidelines. It is also recognized as an alternative regimen in treatment-naïve and non-direct-acting antiviral-experienced kidney transplant patients with genotype 1 or 4 with or without compensated cirrhosis. The guidelines have not been updated to reflect the lower age indication approved with Zepatier.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zepatier. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zepatier as well as the monitoring required for adverse events and long-term efficacy, approval requires Zepatier to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Zepatier is recommended in those who meet one of the following criteria:

FDA-Approved Indications

82. Chronic Hepatitis C Virus (HCV) Genotype 1a. Approve for the duration noted if the patient meets the following criteria (A, B, and C):
- **A)** Patient meets ONE of the following conditions (i or ii):
  - **i.** Patient is ≥ 12 years of age; OR
  - **ii.** Patient weighs ≥ 30 kg; AND
- **B)** Patient meets ONE of the following criteria (i or ii):
  - **i.** Approve for 12 weeks if the patient meets ONE of the following conditions (a or b):
    - **a)** Patient meets both of the following [(1) and (2)]:
      - **(1)** Patient is treatment-naïve, OR patient has previously been treated with pegylated interferon + ribavirin *only*; AND
      - **(2)** Patient does NOT have a baseline NS5A polymorphism at ONE (or more) of the following the amino acid positions: 28, 30, 31, or 93; OR
    - **b)** Patient meets both of the following [(1) and (2)]:
      - **(1)** Patient has previously been treated with pegylated interferon + ribavirin and an HCV protease inhibitor; AND
      - **(2)** The medication will be prescribed in combination with ribavirin; OR
  - **ii.** Approve for 16 weeks if the patient meets the following criteria (a, b, and c):
    - **a)** Patient meets one of the following [(1) or (2)]:
      - **(1)** Patient is treatment-naïve; OR
      - **(2)** Patient has previously been treated with pegylated interferon + ribavirin *only*; AND
    - **b)** Patient has a baseline NS5A polymorphism at ONE (or more) of the following amino acid positions: 28, 30, 31, or 93; AND
    - **c)** The medication will be prescribed in combination with ribavirin; AND
- **C)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

83. Chronic Hepatitis C Virus (HCV) Genotype 1b. Approve for 12 weeks if the patient meets the following criteria (A, B, and C):
- **A)** Patient meets ONE of the following conditions (i or ii):
  - **i.** Patient is ≥ 12 years of age; OR
  - **ii.** Patient weighs ≥ 30 kg; AND
- **B)** Patient meets ONE of the following conditions (i or ii):
  - **i.** Patient meets one of the following criteria (a or b):
    - **a)** Patient is treatment-naïve; OR
    - **b)** Patient has previously been treated with pegylated interferon + ribavirin *only*; OR
  - **ii.** Patient meets the following criteria (a and b):

a) Patient has previously been treated with pegylated interferon + ribavirin + an HCV protease inhibitor; AND
b) The medication will be prescribed in combination with ribavirin; AND

C) The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

84. Chronic Hepatitis C Virus (HCV) Genotype 4. Approve for the duration noted if the patient meets the following criteria (A, B, and C):

A) Patient meets ONE of the following criteria (i or ii):
i. Patient is ≥ 12 years of age; OR
ii. Patient weighs ≥ 30 kg; AND

B) Patient meets ONE of the following criteria (i or ii):
i. Patient is treatment-naïve: Approve for 12 weeks; OR
ii. Approve for 16 weeks if the patient meets both of the following (a and b):
a) Patient has previously been treated with pegylated interferon and ribavirin for HCV; AND
b) The medication will be prescribed in combination with ribavirin; AND

C) The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

Other Uses with Supportive Evidence

85. Patient is Currently Receiving Zepatier. Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications). Approve the duration described above to complete a course of therapy (e.g., a patient who should receive 12 weeks and has received 3 weeks should be approved for 9 weeks to complete their 12-week course).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zepatier is not recommended in the following situations:

1. **Hepatitis C Virus (HCV), Child-Pugh Class B or Child-Pugh Class C Liver Disease (Moderate or Severe Hepatic Impairment).** Zepatier is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C).[1]

2. **Hepatitis C Virus (HCV) [Any Genotype], Combination with Any Other Direct-Acting Antivirals (Not Including Ribavirin).** Zepatier provides a complete antiviral regimen for patients with genotype 1 and 4 chronic HCV.

3. **Life Expectancy Less Than 12 Months Due to Non-Liver Related Comorbidities.** According to AASLD guidance, little evidence exists to support initiation of HCV treatment in patients with limited life expectancy (less than 12 months) due to non-liver-related comorbid conditions.[2] For these patients, the benefits of HCV treatment are unlikely to be realized, and palliative care strategies should take precedence.

4. **Pediatric Patients (Age < 12 Years or < 30 kg).** The safety and efficacy of Zepatier have not been established in pediatric patients < 12 years of age or < 30 kg.[1] Guidelines recommend Harvoni (ledipasvir/sofosbuvir tablets) in pediatric patients with genotypes 1 or 4 chronic HCV.[2]

5. **Retreatment with Zepatier in Patients Who Have Previously Received Zepatier.** Zepatier is not recommended. This includes retreatment in prior null responders, prior partial responders, prior relapse

patients, and patients who have not completed a course of therapy due to an adverse reaction or for other reasons.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Hepatology – Givlaari Prior Authorization Policy
- Givlaari™ (givosiran subcutaneous injection – Alnylam)

REVIEW DATE: 10/18/2023

OVERVIEW

Givlaari, an aminolevulinate synthase 1-directed small interfering RNA, is indicated for the treatment of patients ≥ 18 years of age with **acute hepatic porphyria** (AHP).[1]

Givlaari is a double-stranded small interfering RNA that causes degradation of aminolevulinate synthase 1 (ALAS1) mRNA in hepatocytes through RNA interference, reducing the elevated levels of liver ALAS1 mRNA.[1] This leads to reduced circulating levels of neurotoxic intermediates aminolevulinic acid and porphobilinogen, factors associated with attacks and other disease manifestations of AHP. In the pivotal trial, inclusion criteria specified a minimum of two porphyria attacks requiring hospitalization, urgent healthcare visit, or intravenous hemin administration at home in the 6 months prior to study entry. Hemin use during the study was permitted for the treatment of acute porphyria attacks.

Disease Overview

Porphyria is a group of metabolic disorders caused by abnormalities in the chemical steps that lead to the production of heme.[2] AHPs are a subgroup of porphyrias in which the enzyme deficiency occurs within the liver.[3] AHPs include acute intermittent porphyria (AIP), variegate porphyria (VP), 5-aminolevulinic acid dehydratase deficiency porphyria (ALAD), and hereditary coproporphyria (HCP) and are characterized by acute neurovisceral symptoms with or without cutaneous manifestations.[3,4] Symptoms and treatments for AIP, VP, ALAD, and HCP are similar; however, VP and HCP patients often develop photosensitivity. Signs and symptoms of AHP usually occur intermittently and include abdominal pain, constipation, muscle weakness, pain in the arms and legs, insomnia, emotional complications, rapid pulse, and high blood pressure. Although most symptomatic patients with AHP have complete resolution of their symptoms between attacks, those with numerous recurrences may develop chronic pain.

Dosing Information

The recommended dose is 2.5 mg/kg administered by subcutaneous injection once monthly by a healthcare professional only.

Guidelines

The Porphyrias Consortium of the National Institutes of Health's Rare Diseases Clinical Research Network has developed recommendations for evaluation and long-term management of AHPs (2017).[5] Initial assessments should include diagnostic confirmation by biochemical testing, subsequent genetic testing to determine the specific AHP, and a complete medical history and physical examination. Preventative measures should be taken to prevent attacks. Hemin therapy (e.g., Panhematin® [hemin injection for intravenous infusion]) is recommended for preventative management in AHP and treatment during acute attacks. Patients with ≥ four attacks per year are candidates for either prophylactic or "on demand" infusions. The need for ongoing prophylaxis should be assessed every 6 to 12 months. Repeated long-term treatment with hemin therapy can lead to iron overload and contribute to hepatic damage and fibrosis. Carbohydrate loading (glucose tablets or dextrose solutions) has been used in early stages of an acute attack, but there are no clear data showing a benefit. Women with AHP can develop cyclic attacks correlated with the menstrual cycle. Options to prevent these attacks include recognizing and removing exacerbating

factors, a gonadotropin releasing-hormone analog, switching to a low dose hormonal contraceptive, or prophylactic hemin therapy infusions.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Givlaari. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Givlaari as well as the monitoring required for adverse events and long-term efficacy, approval requires Givlaari to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Givlaari is recommended in those who meet the following criteria:

FDA-Approved Indication

86. Acute Hepatic Porphyria. Approve for 1 year if the patient meets the following (A, B, C, and D):

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Diagnosis of acute hepatic porphyria was confirmed by both of the following (i and ii):
  - **i.** Patient demonstrated clinical features associated with acute hepatic porphyria; AND
    Note: Examples of clinical features associated with acute intermittent porphyria include neurovisceral symptoms, blistering lesions, hepatic involvement, peripheral neuropathy, abdominal pain, constipation, muscle weakness, pain in the arms and legs.
  - **ii.** Patient meets one of the following (a or b):
    - **a)** Elevated urinary aminolevulinic acid (ALA) greater than the upper limit of normal; OR
    - **b)** Elevated urinary porphobilinogen (PBG) greater than the upper limit of normal; AND
- **C)** Prior to starting treatment with Givlaari, the patient has a of one porphyria attack in the last 6 months that required a hospitalization, urgent healthcare visit, or intravenous hemin administration at home; AND
- **D)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, or a physician who specializes in acute hepatic porphyria.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Givlaari is not recommended in the following situations:

138. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Hepatology – Livmarli Prior Authorization Policy
- Livmarli™ (maralixibat oral solution – Mirum)

REVIEW DATE: 10/18/2023

OVERVIEW

Livmarli, an ileal bile acid transporter (IBAT) inhibitor, is indicated for the treatment of cholestatic pruritus in patients ≥ 3 months of age with **Alagille syndrome**.[1]

Disease Overview

Alagille syndrome is a rare liver disease defined by genetic deletion or mutation affecting bile acid transporters (e.g., deletion or mutation of the *JAG1* gene or *NOTCH2* gene).[2-4] Main clinical manifestations include cholestasis, pruritus, and jaundice. Progression of the disease can cause liver fibrosis, cirrhosis, or end-stage liver disease and leads to death at an early age in life (infancy to adolescence). Pruritus is a common symptom in patients with Alagille syndrome and the pathophysiology of pruritus in these patients is not completely understood.[1] Although the complete mechanism by which Livmarli improves pruritus in patients with Alagille syndrome is unknown, it may involve inhibition of the IBAT, which results in decreased reuptake of bile salts, as observed by a decrease in serum bile acids. Cholestyramine, rifampicin, and ursodeoxycholic acid (ursodiol) have been used off-label for decades to alleviate symptoms related to Alagille syndrome.[2-5]

Clinical Efficacy

The efficacy of Livmarli was evaluated in one study that involved an 18-week open-label treatment period, followed by a 4-week randomized, double-blind, placebo-controlled drug withdrawal period. The study was conducted in 31 pediatric patients with Alagille syndrome (1 year to 15 years of age) with cholestasis and pruritus. Patients enrolled all had *JAG1* mutation, elevated serum bile acid concentration, and presence of at least moderate pruritus at baseline. Patients treated with Livmarli demonstrated greater improvement in pruritus compared with placebo. Safety and tolerability in infants less than 1 year of age was assessed in a 13 week, open label, phase 2 study of 12 patients. Livmarli was well tolerated with treatment emergent adverse events, which were mostly Grade 1 and unrelated to therapy. [1]

Safety

Livmarli was not evaluated in patients with cirrhosis.[1] Monitor for liver test abnormalities; permanently discontinue Livmarli if a patient progresses to portal hypertension or experiences a hepatic decompensation event (e.g., variceal hemorrhage, ascites, hepatic encephalopathy).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Livmarli. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Livmarli as well as the monitoring required for adverse events and long-term efficacy, approval requires Livmarli to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Livmarli is recommended in those who meet the following criteria:

FDA-Approved Indication

87. Alagille Syndrome. Approve for the duration noted if the patient meets one of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets all of the following (i, ii, iii, iv, v, vi and vii):

i. Patient is ≥ 3 months of age; AND

ii. Patient has moderate-to-severe pruritus, according to prescriber; AND

iii. Diagnosis of Alagille syndrome was confirmed by genetic testing demonstrating a *JAG1* or *NOTCH2* deletion or mutation; AND

iv. Patient has a serum bile acid concentration above the upper limit of the normal reference range for the reporting laboratory; AND

v. Patient has tried at least two systemic medications for Alagille syndrome, unless contraindicated; AND

26. Note: Systemic medications for Alagille syndrome include cholestyramine, rifampicin, and ursodeoxycholic acid (ursodiol).

vi. Patient does not have any of the following (a, b, or c):

a) Cirrhosis; OR

b) Portal hypertension; OR

c) History of a hepatic decompensation event; AND

27. Note: Examples of a hepatic decompensation event include variceal hemorrhage, ascites, and hepatic encephalopathy.

vii. The medication is prescribed by or in consultation with a hepatologist, gastroenterologist, or a physician who specializes in Alagille syndrome.

B) Patient is Currently Receiving Livmarli. Approve for 1 year if the patient meets all of the following (i, ii, and iii):

i. Patient does not have any of the following (a, b, or c):

a) Cirrhosis; OR

b) Portal hypertension; OR

c) of a hepatic decompensation event; AND

28. Note: Examples of a hepatic decompensation event include variceal hemorrhage, ascites, and hepatic encephalopathy.

ii. Patient had response to therapy, as determined by the prescriber; AND

29. Note: Examples of response to therapy include decrease in serum bile acids and decrease in pruritus.

iii. The medication is prescribed by or in consultation with a hepatologist, gastroenterologist, or a physician who specializes in Alagille syndrome.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Livmarli is not recommended in the following situations:

139. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Hepatology – Ocaliva Prior Authorization Policy
- Ocaliva® (obeticholic acid tablets – Intercept Pharmaceuticals)

REVIEW DATE: 07/19/2023

OVERVIEW

Ocaliva, a faresoid X receptor agonist, is indicated for the treatment of **primary biliary cholangitis** in adults without cirrhosis, or with compensated cirrhosis who do not have evidence of portal hypertension.[1] It is specifically indicated to be given either in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.

Guidelines

The American Association for the Study of Liver Diseases (AASLD) guidelines for primary biliary cholangitis (2018) state that the diagnosis can be confirmed when patients meet two of the following criteria: 1) there is cholestasis as evidenced by alkaline phosphatase elevation; 2) anti-mitochondrial antibodies are present, or if negative for anti-mitochondrial antibodies, other primary biliary cholangitis-specific autoantibodies, including sp100 or gp210, are present; 3) there is histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts. It is specifically noted that diagnosis in a patient who is negative for anti-mitochondrial antibodies does not require a liver biopsy if other diagnostic criteria are met.[4] Treatment with UDCA (available in the US as ursodiol) is the recommended treatment for patients with primary biliary cholangitis who have abnormal liver enzyme values regardless of histologic stage.[3] Following 12 months of UDCA therapy, the patient should be evaluated to determine if second-line therapy is appropriate. It is estimated that up to 40% of patients have an inadequate response to UDCA; Ocaliva should be considered for these patients. An update to the 2018 AASLD guidelines for primary biliary cholangitis (2021) provide two updated recommendations:[9] 1) Fibrates can be considered as off-label alternatives for patients with primary biliary cholangitis and inadequate response to UDCA. However, fibrates are discouraged in patients with decompensated liver disease; and 2) Ocaliva is contraindicated in patients with advanced cirrhosis, defined as cirrhosis with current or prior evidence of liver decompensation (e.g., encephalopathy, coagulopathy) or portal hypertension (e.g., ascites, gastroesophageal varices, or persistent thrombocytopenia). In addition, the AASLD recommends careful monitoring of any patient with cirrhosis, even if not advanced, receiving Ocaliva.

The European Association for the Study of the Liver guidelines for diagnosis and management of patients with primary biliary cholangitis (2017) make similar recommendations.[7]

Safety

Ocaliva has a Boxed warning regarding hepatic decompensation and failure in patients with primary biliary cholangitis and cirrhosis.[1] Ocaliva is contraindicated in patients with primary biliary cholangitis with decompensated cirrhosis and patients with a prior decompensation event. It is also contraindicated in patients with compensated cirrhosis with evidence of portal hypertension (e.g., ascites, gastroesophageal varices, and persistent thrombocytopenia) as well as those with complete biliary obstruction.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Ocaliva. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ocaliva as well as the monitoring required for adverse events and long-term efficacy, approval requires Ocaliva to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Ocaliva is recommended in those who meet the following criteria:

FDA-Approved Indication

42. Primary Biliary Cholangitis. Approve Ocaliva for the duration noted if the patient meets one of the following (A or B):
Note: Primary Biliary Cholangitis is also known as Primary Biliary Cirrhosis.
3. Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, and iv):
i. Patient is ≥ 18 years of age; AND
ii. According to the prescriber, the patient has a diagnosis of primary biliary cholangitis as defined by TWO of the following (TWO of a, b, or c):
a) Alkaline phosphatase is elevated above the upper limit of normal as defined by normal laboratory reference values; OR
b) Positive anti-mitochondrial antibodies or other primary biliary cholangitis-specific auto-antibodies, including sp100 or gp210, if anti-mitochondrial antibodies are negative; OR
c) Histologic evidence of primary biliary cholangitis from a liver biopsy; AND
iii. Patient meets ONE of the following (a or b):
a) Patient has been receiving ursodiol therapy for ≥ 1 year and has had an inadequate response according to the prescriber; OR
b) According to the prescriber the patient is unable to tolerate ursodiol therapy; AND
Note: Examples of ursodiol therapy include ursodiol generic tablets and capsules, Urso 250, Urso Forte, and Actigall.
iv. Patient meets one of the following (a or b):
a) Patient does not have cirrhosis; OR
b) Patient has compensated cirrhosis without evidence of portal hypertension; AND
Note: Examples of evidence of portal hypertension include ascites, gastroesophageal varices, and persistent thrombocytopenia. Ocaliva is contraindicated in these patients.
v. The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, or liver transplant physician.
4. Patient is Currently Receiving Therapy. Approve for 1 year if the patient meets both of the following (i and ii):
i. Patient meets one of the following (a or b):
a) Patient does not have cirrhosis; OR
b) Patient has compensated cirrhosis without evidence of portal hypertension; AND
Note: Examples of evidence of portal hypertension include ascites, gastroesophageal varices, and persistent thrombocytopenia. Ocaliva is contraindicated in these patients.
ii. Patient has responded to Ocaliva as determined by the prescriber.

Note: Examples of a response to Ocaliva therapy are improved biochemical markers of primary biliary cholangitis (e.g., alkaline phosphatase [ALP], bilirubin, gamma-glutamyl transpeptidase [GGT], aspartate aminotransferase [AST], alanine aminotransferase [ALT]).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ocaliva is not recommended in the following situations:

26. Alcoholic Liver Disease. There are no data available to support the use of Ocaliva in patients with alcoholic hepatitis. Ocaliva is not FDA-approved for this indication and current alcoholic liver disease guidelines from AASLD (2019) do not make recommendations regarding therapy with Ocaliva.[1,8] Additional well-controlled studies are needed.

27. Nonalcoholic Fatty Liver Disease (NAFLD), including Nonalcoholic Fatty Liver (NAFL) or Nonalcoholic Steatohepatitis (NASH). Ocaliva is not FDA-approved for this indication and current NAFLD guidelines from AASLD (2023) do not recommend the off-label use of obeticholic acid to treat NASH until additional safety and efficacy data become available.[1,8]

28. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Hepatology – Bylvay Prior Authorization Policy
- Bylvay™ (odevixibat capsules and oral pellets – Albireo Pharma)

REVIEW DATE: 07/19/2023

OVERVIEW

Bylvay, an ileal bile acid transporter (IBAT) inhibitor, is indicated for the treatment of:
- Pruritus in patients ≥ 3 months of age with **progressive familial intrahepatic cholestasis** (PFIC).[1]
- Cholestatic pruritus in patients ≥ 12 months of age with **Alagille syndrome** (ALGS).[1]

Disease Overview

PFIC is a group of rare, autosomal recessive liver diseases defined by genetic mutations affecting bile acid transporters (e.g., mutation of the *ATP8B1* gene, *ABCB11* gene, *ABCB4* gene, *TJP2* gene, *NR1H4* gene, and *MYO5B* gene).[2-4] **ALGS** is a rare liver disease defined by genetic deletion or mutation affecting bile acid transporters (e.g., deletion or mutation of the *JAG1* gene or *NOTCH2* gene).[5,8,9] Progression of both diseases can cause liver fibrosis, cirrhosis, or end-stage liver disease and leads to death at an early age in life (infancy to adolescence).

Cholestasis, jaundice, and pruritus are common symptoms in patients with PFIC and ALGS.[8,9] Although the complete mechanism by which Bylvay improves pruritus in these patients is unknown, it may involve inhibition of the IBAT, which results in decreased reuptake of bile salts, as observed by a decrease in serum bile acids. Cholestyramine, rifampicin, and ursodeoxycholic acid (ursodiol) have been used off-label for decades to alleviate symptoms related to PFIC and ALGS.[5,6,9] Cholestyramine, ursodeoxycholic acid, rifampicin, naltrexone, and sertraline are recommended in clinical practice guidelines from the European Association for the Study of the Liver (2009).[7]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Bylvay. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Bylvay as well as the monitoring required for adverse events and long-term efficacy, approval requires Bylvay to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Bylvay is recommended in those who meet the following criteria:

FDA-Approved Indication

88. Progressive Familial Intrahepatic Cholestasis. Approve for the duration noted if the patient meets one of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets all of the following (i, ii, iii, iv, v, vi and vii):

i. Patient is ≥ 3 months of age; AND
ii. Patient has moderate-to-severe pruritus, according to the prescriber; AND
iii. Diagnosis of progressive familial intrahepatic cholestasis was confirmed by genetic testing demonstrating a gene mutation affiliated with progressive familial intrahepatic cholestasis; AND
Note: Gene mutations affiliated with progressive familial intrahepatic cholestasis include the *ATP8B1* gene, *ABCB11* gene, *ABCB4* gene, *TJP2* gene, *NR1H4* gene, and *MYO5B* gene.
iv. Patient has a serum bile acid concentration above the upper limit of the normal reference range for the reporting laboratory; AND
v. Patient has tried at least two systemic medications for progressive familial intrahepatic cholestasis, unless contraindicated; AND
Note: Systemic medications for progressive familial intrahepatic cholestasis include cholestyramine, naltrexone, rifampicin, sertraline, and ursodeoxycholic acid (ursodiol).
vi. Patient does not have any of the following (a, b, or c):
a) Cirrhosis; OR
b) Portal hypertension; OR
c) History of a hepatic decompensation event; AND
Note: Examples of a hepatic decompensation event include variceal hemorrhage, ascites, and hepatic encephalopathy.
vii. The medication is prescribed by or in consultation with a hepatologist, gastroenterologist, or a physician who specializes in progressive familial intrahepatic cholestasis.

C) Patient is Currently Receiving Bylvay. Approve for 1 year if the patient meets all of the following (i, ii, and iii):
iii. Patient does not have any of the following (a, b, or c):
a) Cirrhosis; OR
b) Portal hypertension; OR
c) History of a hepatic decompensation event; AND
Note: Examples of a hepatic decompensation event include variceal hemorrhage, ascites, and hepatic encephalopathy.
iv. Patient had response to therapy, as determined by the prescriber; AND
Note: Examples of response to therapy include decrease in serum bile acids and decrease in pruritus.
iv. The medication is prescribed by or in consultation with a hepatologist, gastroenterologist, or a physician who specializes in progressive familial intrahepatic cholestasis.

89. Alagille Syndrome. Approve for the duration noted if the patient meets one of the following (A or B):
A) Initial Therapy. Approve for 6 months if the patient meets all of the following (i, ii, iii, iv, v, vi and vii):
i. Patient is ≥ 12 months of age; AND
ii. Patient has moderate-to-severe pruritus, according to the prescriber; AND
iii. Diagnosis of Alagille syndrome was confirmed by genetic testing demonstrating a *JAG1* or *NOTCH2* deletion or mutation; AND
iv. Patient has a serum bile acid concentration above the upper limit of the normal reference range for the reporting laboratory; AND
v. Patient has tried at least two systemic medications for Alagille syndrome, unless contraindicated; AND
Note: Systemic medications for Alagille syndrome include cholestyramine, naltrexone, rifampicin, sertraline, and ursodeoxycholic acid (ursodiol).
vi. Patient does not have any of the following (a, b, or c):
a) Cirrhosis; OR

b) Portal hypertension; OR
c) History of a hepatic decompensation event; AND
Note: Examples of a hepatic decompensation event include variceal hemorrhage, ascites, and hepatic encephalopathy.

vii. The medication is prescribed by or in consultation with a hepatologist, gastroenterologist, or a physician who specializes in Alagille syndrome.

D) Patient is Currently Receiving Bylvay. Approve for 1 year if the patient meets all of the following (i, ii, and iii):

i. Patient does not have any of the following (a, b, or c):
a) Cirrhosis; OR
b) Portal hypertension; OR
c) of a hepatic decompensation event; AND
Note: Examples of a hepatic decompensation event include variceal hemorrhage, ascites, and hepatic encephalopathy.

ii. Patient had response to therapy, as determined by the prescriber; AND
Note: Examples of response to therapy include decrease in serum bile acids and decrease in pruritus.

iii. The medication is prescribed by or in consultation with a hepatologist, gastroenterologist, or a physician who specializes in Alagille syndrome.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Bylvay is not recommended in the following situations:

140. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Hereditary Angioedema – C1 Esterase Inhibitors (Intravenous) Prior Authorization Policy
- Berinert® (C1 esterase inhibitor [human] intravenous infusion – CSL Behring)
- Cinryze® (C1 esterase inhibitor [human] intravenous infusion – Takeda)
- Ruconest® (C1 esterase inhibitor [recombinant] intravenous infusion – Pharming)

REVIEW DATE: 09/20/2023

OVERVIEW

Berinert, Cinryze, and Ruconest are C1 esterase inhibitor (C1-INH) replacement therapies for hereditary angioedema (HAE).[1-3] Cinryze and Berinert are human plasma-derived C1-INH; Ruconest is a recombinant C1-INH purified from milk of transgenic rabbits. Labeled indications are as follows:

- Berinert is indicated for the **treatment of acute abdominal, facial, or laryngeal HAE attacks** in adults and pediatric patients.[1]
- Cinryze is indicated for routine **prophylaxis against HAE attacks** in patients ≥ 6 years of age.[2]
- Ruconest is indicated for the **treatment of acute HAE attacks** in adults and adolescent patients.[3]

Of note, although Cinryze is labeled for use in the prophylactic setting and Berinert is labeled for use in the acute treatment setting, use of Cinryze in the acute setting and Berinert in the prophylactic setting has been reported in the literature.[4,5]

Guidelines

Acute Treatment of HAE Attacks

According to US HAE Association Medical Advisory Board Guidelines (2020), when HAE is suspected based on clinical presentation, appropriate testing includes measurement of the serum C4 level, C1-INH antigenic level, and C1-INH functional level.[6] Low C4 plus low C1-INH antigenic or functional level is consistent with a diagnosis of HAE types I/II. The goal of acute therapy is to minimize morbidity and prevent mortality from an ongoing HAE attack. Patients must have ready access to effective on-demand medication to administer at the onset of an HAE attack. All HAE attacks are eligible for treatment, irrespective of the location of swelling or severity of the attack. First-line treatments include plasma-derived C1-INH, Ruconest, Kalbitor® (ecallantide subcutaneous [SC] injection), and icatibant (Firazyr®, generic).

In guidelines from the World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) [2021], it is recommended that all attacks be treated with either IV C1-INH, Kalbitor, or icatibant (evidence level A for all).[7] Regarding IV C1-INH, it is noted that Berinert and Cinryze are both plasma-derived products available for this use, although indications vary globally. It is essential that patients have on-demand medication to treat all attacks; thus, the guidelines recommend that patients have and carry medication for treatment of at least two attacks.

Long-Term Prophylaxis

US HAE Association Medical Advisory Board Guidelines (2020) note the decision on when to use long-term prophylaxis cannot be made on rigid criteria but should reflect the needs of the individual patient.[6] First-line medications for HAE I/II include intravenous (IV) C1-INH, Haegarda® (C1-INH [human] SC injection), or Takhzyro® (landelumab-flyo SC injection). The guideline was written prior to approval of Orladeyo® (berotralstat capsules).

According to WAO/EAACI guidelines (2021), it is recommended to evaluate for long-term prophylaxis at every visit, taking disease activity, burden, and control as well as patient preference into consideration.[7] The following therapies are supported as first-line options for long-term prophylaxis: plasma-derived C1-INH (87% agreement), Takhzyro (89% agreement), and Orladeyo (81% agreement). With regard to plasma-derived C1-INH, it is noted that Haegarda provided very good and dose-dependent preventative effects on the occurrence of HAE attacks; the subcutaneous route may provide more convenient administration and maintain improved steady-state plasma concentrations compared with the IV route. Of note, androgens are not recommended in the first-line setting for long-term prophylaxis. Recommendations are not made regarding long-term prophylaxis in HAE with normal C1-INH.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Berinert, Cinryze, and Ruconest. Because of the specialized skills required for evaluation and diagnosis of patients treated with Berinert, Cinryze, or Ruconest, as well as monitoring required for adverse events and long-term efficacy, approval requires the medication to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. A patient who has previously met initial therapy criteria for Berinert, Cinryze, and Ruconest for the requested indication under the Coverage Review Department and is currently receiving the requested therapy is only required to meet the continuation therapy criteria (i.e., currently receiving Berinert, Cinryze, or Ruconest). If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Berinert, Cinryze, or Ruconest, initial therapy criteria must be met.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory records, and prescription claims records.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Berinert or Cinryze is recommended in those who meet one of the following criteria:

FDA-Approved Indications

35. Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Prophylaxis. Approve Berinert or Cinryze for 1 year if the patient meets one of the following (A or B):

- **A)** Initial therapy. Approve if the patient meets both of the following (i and ii):
  - **i.** Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
    Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
    - **a)** Patient has low levels of functional C1-INH protein (< 50% of normal) at baseline, as defined by the laboratory reference values **[documentation required]**; AND
    - **b)** Patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values **[documentation required]**; AND
  - **ii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.
- **B)** Patient is currently receiving Berinert or Cinryze prophylaxis. Approve if the patient meets all of the following (i, ii, and iii):

Note: If the patient is currently receiving the requested therapy, but has not previously received approval of Berinert or Cinryze for this indication through the Coverage Review Department, review under criteria for Initial Therapy.

i. Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND
Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.

ii. According to the prescriber, the patient has had a favorable clinical response since initiating Berinert or Cinryze prophylactic therapy compared with baseline (i.e., prior to initiating prophylactic therapy); AND
Note: Examples of a favorable clinical response include decrease in HAE acute attack frequency, decrease in HAE attack severity, or decrease in duration of HAE attacks.

iii. The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

36. Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Treatment of Acute Attacks. Approve Berinert or Cinryze for 1 year if the patient meets one of the following (A or B):

A) Initial therapy. Approve if the patient meets both of the following (i and ii):

i. Patient has HAE type I or type II as confirmed by following (a and b):
Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.

a) Patient has low levels of functional C1-INH protein (< 50% of normal) at baseline, as defined by the laboratory reference values **[documentation required]**; AND

b) Patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values **[documentation required]**; AND

ii. The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

B) Patient who has treated previous acute HAE attacks with Berinert or Cinryze. Approve if the patient meets all of the following (i, ii, and iii):
Note: If the patient is currently receiving the requested therapy, but has not previously received approval of Berinert or Cinryze for this indication through the Coverage Review Department, review under criteria for Initial Therapy.

i. Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND
Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.

ii. According to the prescriber, the patient has had a favorable clinical response with Berinert or Cinryze treatment; AND
Note: Examples of a favorable clinical response include decrease in the duration of HAE attacks, quick onset of symptom relief, complete resolution of symptoms, or decrease in HAE acute attack frequency or severity.

iii. The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

II. Coverage of Ruconest is recommended in those who meet the following criteria:

FDA-Approved Indication

1. Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Treatment of Acute Attacks. Approve Ruconest for 1 year if the patient meets one of the following (A or B):

A) Initial therapy. Approve if the patient meets both of the following (i and ii):

i. Patient has HAE type I or type II as confirmed by the following (a and b):

Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.

a) Patient has low levels of functional C1-INH protein (< 50% of normal) at baseline, as defined by the laboratory reference values **[documentation required]**; AND

b) Patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values **[documentation required]**; AND

ii. The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

B) Patient who has treated previous acute HAE attacks with Ruconest. Approve if the patient meets all of the following (i, ii, and iii):

Note: If the patient is currently receiving the requested therapy, but has not previously received approval of Ruconest for this indication through the Coverage Review Department, review under criteria for Initial Therapy.

i. Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND

Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.

ii. According to the prescriber, the patient has had a favorable clinical response with Ruconest treatment; AND

Note: Examples of a favorable clinical response include decrease in the duration of HAE attacks, quick onset of symptom relief, complete resolution of symptoms, or decrease in HAE acute attack frequency or severity.

iii. The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Berinert, Cinryze, or Ruconest is not recommended in the following situations:

29. Hereditary Angioedema (HAE) Prophylaxis (Ruconest ONLY). Ruconest is not FDA-approved for prophylaxis of HAE attacks. A small (n = 32) Phase II, randomized, double-blind, placebo-controlled trial in adults and adolescents ≥ 13 years of age showed efficacy of Ruconest over placebo for reducing mean monthly rate of HAE attacks ($P < 0.0001$).[8] At this time, evidence is not sufficient to support Ruconest use for HAE prophylaxis.

Note: This Condition Not Recommended for Approval does not apply to Berinert or Cinryze.

30. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

241. Berinert® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; September 2021.
242. Cinryze® intravenous infusion [prescribing information]. Lexington, MA: Takeda; January 2021.
243. Ruconest® intravenous infusion [prescribing information]. Warren, NJ: Pharming; April 2020.
244. Zuraw BL. Hereditary angioedema. *N Engl J Med*. 2008;359:1027-1036.
245. Craig T, Shapiro R, Vegh A, et al. Efficacy and safety of an intravenous C1-inhibitor concentrate for long-term prophylaxis in hereditary angioedema. *Allergy Rhinol (Providence)*. 2017;8(1):13-19.
246. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3.
247. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema: the 2021 revision and update. *Allergy*. 2022;77(7):1961-1990.
248. Riedl MA, Grivcheva-Panovska V, Moldovan D, et al. Recombinant human C1 esterase inhibitor for prophylaxis of hereditary angio-oedema: a phase 2, multicentre, randomised, double-blind, placebo-controlled crossover trial. *Lancet*. 2017;390:1595-1602.

PRIOR AUTHORIZATION POLICY

POLICY: Hereditary Angioedema – C1 Esterase Inhibitors (Subcutaneous) Prior Authorization Policy
- Haegarda® (C1 esterase inhibitor [human] subcutaneous injection – CSL Behring)

REVIEW DATE: 09/20/2023

OVERVIEW

Haegarda, a human plasma-derived C1 esterase inhibitor (C1-INH), is indicated for **routine prophylaxis to prevent hereditary angioedema (HAE) attacks** in adults and pediatric patients ≥ 6 years of age.[1]

Guidelines

According to US HAE Association Medical Advisory Board Guidelines (2020), when HAE is suspected based on clinical presentation, appropriate testing includes measurement of the serum C4 level, C1-INH antigenic level, and C1-INH functional level.[2] Low C4 plus low C1-INH antigenic or functional level is consistent with a diagnosis of HAE types I/II. The decision on when to use long-term prophylaxis cannot be made on rigid criteria but should reflect the needs of the individual patient. First-line medications for HAE I/II include intravenous C1-INH, Haegarda, or Takhzyro® (lanadelumab-flyo subcutaneous injection). The guideline was written prior to approval of Orladeyo® (berotralstat capsules).

According to World Allergy Organization/European Academy of Allergy and Clinical Immunology guidelines (2021), it is recommended to evaluate for long-term prophylaxis at every visit, taking disease activity, burden, and control as well as patient preference into consideration.[3] The following therapies are supported as first-line options for long-term prophylaxis: plasma-derived C1-INH (87% agreement), Takhzyro (89% agreement), and Orladeyo (81% agreement). With regard to plasma-derived C1-INH, it is noted that Haegarda provided very good and dose-dependent preventative effects on the occurrence of HAE attacks; the subcutaneous route may provide more convenient administration and maintain improved steady-state plasma concentrations compared with the intravenous route. Of note, androgens are not recommended in the first-line setting for long-term prophylaxis. Recommendations are not made regarding long-term prophylaxis in HAE with normal C1-INH.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Haegarda. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Haegarda as well as the monitoring for adverse events and long-term efficacy, approval requires Haegarda to be prescribed by or in consultation with a physician who specializes in the condition being treated. A patient who has previously met initial therapy criteria for Haegarda for the requested indication under the Coverage Review Department and is currently receiving the requested therapy is only required to meet the continuation therapy criteria (i.e., currently receiving Haegarda). If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Haegarda, initial therapy criteria must be met.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory records, and prescription claims records.
Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Haegarda is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Prophylaxis.** Approve Haegarda for 1 year if the patient meets one of the following (A or B):
   - **C)** Initial therapy. Approve if the patient meets both of the following (i and ii):
     - **i.** Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
       Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
       - **a)** Patient has low levels of functional C1-INH protein (< 50% of normal) **at baseline**, as defined by the laboratory reference values **[documentation required]**; AND
       - **b)** Patient has lower than normal serum C4 levels **at baseline**, as defined by the laboratory reference values **[documentation required]**; AND
     - **ii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.
   - **D)** Patient is currently receiving Haegarda prophylaxis. Approve if the patient meets all of the following (i, ii, and iii):
     Note: If the patient is currently receiving the requested therapy, but has not previously received approval of Haegarda for this indication through the Coverage Review Department, review under criteria for Initial Therapy.
     - **i.** Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND
       Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
     - **ii.** According to the prescriber, the patient has had a favorable clinical response since initiating Haegarda prophylactic therapy compared with baseline (i.e., prior to initiating prophylactic therapy); AND
       Note: Examples of a favorable clinical response include decrease in HAE acute attack frequency, decrease in HAE attack severity, or decrease in duration of HAE attacks.
     - **iii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Haegarda is not recommended in the following situations:

31. **Concomitant Use with Other Hereditary Angioedema (HAE) Prophylactic Therapies.** Haegarda has not been studied in combination with other prophylactic therapies for HAE, and combination therapy for long-term prophylactic use is not recommended. Patients may use other medications, including Cinryze® (C1 esterase inhibitor [human] intravenous infusion), for treatment of acute HAE attacks, and for short-term (procedural) prophylaxis.
    Note: Examples of other HAE prophylactic therapies include Cinryze (C1 esterase inhibitor [human] intravenous infusion), Orladeyo (berotralstat capsules), and Takhzyro (lanadelumab-flyo subcutaneous injection).

32. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

249. Haegarda® subcutaneous injection [prescribing information]. Kankakee, IL: CSL Behring; January 2022.
250. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3.
251. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema: the 2021 revision and update. *Allergy*. 2022;77(7):1961-1990.

PRIOR AUTHORIZATION POLICY

POLICY: Hereditary Angioedema – Icatibant Prior Authorization Policy
- Firazyr® (icatibant subcutaneous injection – Takeda, generic)
- Sajazir™ (icatibant subcutaneous injection – Cycle)

REVIEW DATE: 09/20/2023

OVERVIEW

Icatibant is a synthetic decapeptide that is indicated for the **treatment of acute hereditary angioedema (HAE) attacks** in adults ≥ 18 years of age.[1]

Guidelines

According to US HAE Association Medical Advisory Board Guidelines (2020), when HAE is suspected based on clinical presentation, appropriate testing includes measurement of the serum C4 level, C1 esterase inhibitor (C1-INH) antigenic level, and C1-INH functional level.[2] Low C4 plus low C1-INH antigenic or functional level is consistent with a diagnosis of HAE types I/II. The goal of acute therapy is to minimize morbidity and prevent mortality from an ongoing HAE attack. Patients must have ready access to effective on-demand medication to administer at the onset of an HAE attack. All HAE attacks are eligible for treatment, irrespective of the location of swelling or severity of the attack. First-line treatments include plasma-derived C1-INH, Ruconest® (C1-INH [recombinant] intravenous [IV] infusion), Kalbitor® (ecallantide subcutaneous injection), and icatibant.

In guidelines from the World Allergy Organization/European Academy of Allergy and Clinical Immunology (2021), it is recommended that all attacks be treated with either IV C1-INH, Kalbitor, or icatibant (evidence level A for all).[3] Regarding IV C1-INH, it is noted that Berinert® (C1 esterase inhibitor [human] IV infusion) and Cinryze® (C1 esterase inhibitor [human] IV infusion) are both plasma-derived products available for this use, although indications vary globally. It is essential that patients have on-demand medication to treat all attacks; thus, the guidelines recommend that patients have and carry medication for treatment of at least two attacks.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of icatibant. Because of the specialized skills required for evaluation and diagnosis of patients treated with icatibant, approval requires icatibant to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. A patient who has previously met initial therapy criteria for icatibant for the requested indication under the Coverage Review Department and is currently receiving the requested therapy is only required to meet the continuation therapy criteria (i.e., patient who has treated previous HAE attacks with icatibant). If past criteria have not been met under the Coverage Review Department and the patient has treated previous HAE attacks with icatibant, initial therapy criteria must be met.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory records, and prescription claims records.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of icatibant is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Treatment of Acute Attacks.** Approve for 1 year if the patient meets one of the following (A or B):
    - Initial therapy. Approve if the patient meets both of the following (i and ii):
        - Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):

30. Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.

- Patient has low levels of functional C1-INH protein (< 50% of normal) **at baseline**, as defined by the laboratory reference values **[documentation required]**; AND
- Patient has lower than normal serum C4 levels **at baseline**, as defined by the laboratory reference values **[documentation required]**; AND

        - The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.
    - Patient who has treated previous HAE attacks with icatibant. Approve if the patient meets all of the following (i, ii, and iii):

31. Note: If the patient is currently receiving the requested therapy but has not previously received approval of icatibant for this indication through the Coverage Review Department, review under criteria for Initial Therapy.

- Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND

32. Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.

- According to the prescriber, the patient has had a favorable clinical response with icatibant treatment; AND

33. Note: Examples of a favorable clinical response include decrease in the duration of HAE attacks, quick onset of symptom relief, complete resolution of symptoms, or decrease in HAE acute attack frequency or severity.

- The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

34.

35.

36. CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of icatibant is not recommended in the following circumstances:

33. Hereditary Angioedema (HAE) Prophylaxis. Data are not available and icatibant is not indicated for prophylaxis of HAE attacks.

34. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

252. Firazyr® subcutaneous injection [prescribing information]. Lexington, MA: Takeda; October 2021.
253. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3.
254. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema: the 2021 revision and update. *Allergy*. 2022;77(7):1961-1990.

PRIOR AUTHORIZATION POLICY

POLICY: Hereditary Angioedema – Kalbitor Prior Authorization Policy
- Kalbitor® (ecallantide subcutaneous injection – Takeda)

REVIEW DATE: 09/20/2023

OVERVIEW

Kalbitor, a plasma kallikrein inhibitor, is indicated for the **treatment of acute attacks of hereditary angioedema (HAE)** in patients ≥ 12 years of age.[1]

Potentially serious hypersensitivity reactions, including anaphylaxis, have occurred in patients treated with Kalbitor.[1] Kalbitor should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and HAE.

Guidelines

According to US HAE Association Medical Advisory Board Guidelines (2020), when HAE is suspected based on clinical presentation, appropriate testing includes measurement of the serum C4 level, C1 esterase inhibitor (C1-INH) antigenic level, and C1-INH functional level.[2] Low C4 plus low C1-INH antigenic or functional level is consistent with a diagnosis of HAE types I/II. The goal of acute therapy is to minimize morbidity and prevent mortality from an ongoing HAE attack. Patients must have ready access to effective on-demand medication to administer at the onset of an HAE attack. All HAE attacks are eligible for treatment, irrespective of the location of swelling or severity of the attack. First-line treatments include plasma-derived C1-INH, Ruconest® (C1-INH [recombinant] intravenous infusion), Kalbitor, and icatibant.

In guidelines from the World Allergy Organization/European Academy of Allergy and Clinical Immunology (2021), it is recommended that all attacks be treated with either IV C1-INH, Kalbitor, or icatibant (evidence level A for all).[3] Regarding IV C1-INH, it is noted that Berinert® (C1 esterase inhibitor [human] IV infusion) and Cinryze® (C1 esterase inhibitor [human] IV infusion) are both plasma-derived products available for this use, although indications vary globally. It is essential that patients have on-demand medication to treat all attacks; thus, the guidelines recommend that patients have and carry medication for treatment of at least two attacks.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Kalbitor. Because of the specialized skills required for the evaluation and diagnosis of patients treated with Kalbitor, approval requires Kalbitor to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. A patient who has previously met initial therapy criteria for Kalbitor for the requested indication under the Coverage Review Department and is currently receiving the requested therapy, is only required to meet the continuation criteria (i.e., patient who has treated previous acute HAE attacks with Kalbitor). If past criteria have not been met under the Coverage Review Department and the patient has treated previous HAE attacks with Kalbitor, initial therapy criteria must be met.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory records, and prescription claims records.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kalbitor is recommended in those who meet the following criteria:

FDA-Approved Indication

2. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Treatment of Acute Attacks.** Approve Kalbitor for 1 year if the patient meets one of the following (A or B):
    - Initial therapy. Approve if the patient meets both of the following (i and ii):
        - Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):

    Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.

        - Patient has low levels of functional C1-INH protein (< 50% of normal) at baseline, as defined by the laboratory reference values **[documentation required]**; AND
        - Patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values **[documentation required]**; AND
        - The medication is prescribed by or in consultation with an allergist/immunologist or a physician that specializes in the treatment of HAE or related disorders.
    - Patient who has treated previous acute HAE attacks with Kalbitor. Approve if the patient meets all of the following (i, ii, and iii):

    Note: If the patient is currently receiving the requested therapy but has not previously received approval of Kalbitor for this indication through the Coverage Review Department, review under criteria for Initial Therapy.

        - Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND

    Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.

        - According to the prescriber, the patient has had a favorable clinical response with Kalbitor treatment; AND

    Note: Examples of a favorable clinical response include decrease in the duration of HAE attacks, quick onset of symptom relief, complete resolution of symptoms, or decrease in HAE acute attack frequency or severity.

        - The medication is prescribed by or in consultation with an allergist/immunologist or a physician that specializes in the treatment of HAE or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kalbitor is not recommended in the following situations:

5. **Hereditary Angioedema (HAE) Prophylaxis.** Data are not available and Kalbitor is not indicated for the prophylaxis of HAE attacks.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

255. Kalbitor® [prescribing information]. Lexington, MA: Takeda; December 2020.
256. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3.
257. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema: the 2021 revision and update. *Allergy*. 2022;77(7):1961-1990.

PRIOR AUTHORIZATION POLICY

POLICY: Hereditary Angioedema – Orladeyo Prior Authorization Policy
- Orladeyo® (berotralstat capsules – Biocryst)

REVIEW DATE: 09/27/2023

OVERVIEW

Orladeyo, an inhibitor of plasma kallikrein, is indicated for **prophylaxis to prevent attacks of hereditary angioedema (HAE)** in patients ≥ 12 years of age.[1]

Guidelines

According to US HAE Association Medical Advisory Board Guidelines (2020), when HAE is suspected based on clinical presentation, appropriate testing includes measurement of the serum C4 level, C1 esterase inhibitor (C1-INH) antigenic level, and C1-INH functional level.[2] Low C4 plus low C1-INH antigenic or functional level is consistent with a diagnosis of HAE types I/II. The decision on when to use long-term prophylaxis cannot be made on rigid criteria but should reflect the needs of the individual patient. First-line medications for HAE I/II include intravenous C1-INH, Haegarda® (C1-INH [human] subcutaneous injection), or Takhzyro® (lanadelumab-flyo subcutaneous injection). The guideline was written prior to approval of Orladeyo.

According to World Allergy Organization/European Academy of Allergy and Clinical Immunology guidelines (2021), it is recommended to evaluate for long-term prophylaxis at every visit, taking disease activity, burden, and control as well as patient preference into consideration.[3] The following therapies are supported as first-line options for long-term prophylaxis: plasma-derived C1-INH (87% agreement), Takhzyro (89% agreement), and Orladeyo (81% agreement). With regard to plasma-derived C1-INH, it is noted that Haegarda provided very good and dose-dependent preventative effects on the occurrence of HAE attacks; the subcutaneous route may provide more convenient administration and maintains improved steady-state plasma concentrations compared with the intravenous route. Of note, androgens are not recommended in the first-line setting for long-term prophylaxis. Recommendations are not made regarding long-term prophylaxis in HAE with normal C1-INH levels.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Orladeyo. Because of the specialized skills required for evaluation and diagnosis of patients treated with Orladeyo, approval requires Orladeyo to be prescribed by or in consultation with a physician who specializes in the condition being treated. A patient who has previously met initial therapy criteria for Orladeyo for the requested indication under the Coverage Review Department and is currently receiving the requested therapy is only required to meet the continuation therapy criteria (i.e., currently receiving Orladeyo). If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Orladeyo, initial therapy criteria must be met. All approvals are provided for the duration noted below.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory records, and prescription claims records.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Orladeyo is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Prophylaxis.** Approve for 1 year if the patient meets one of the following (A or B):
   - **E)** Initial therapy. Approve if the patient meets all of the following (i, ii, and iii):
     - **i.** Patient is ≥ 12 years of age; AND
     - **ii.** Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
       Note: A diagnosis of HAE with normal C1-INH (also referred to as HAE type III) does NOT satisfy this requirement.
       - **a)** Patient has low levels of functional C1-INH protein (< 50% of normal) at baseline, as defined by the laboratory reference values **[documentation required]**; AND
       - **b)** Patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values **[documentation required]**; AND
     - **iii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.
   - **F)** Patient is currently receiving Orladeyo. Approve if the patient meets all of the following (i, ii, iii, and iv):
     Note: If the patient is currently receiving the requested therapy, but has not previously received approval of Orladeyo for this indication through the Coverage Review Department, review under criteria for Initial Therapy.
     - **i.** Patient is ≥ 12 years of age; AND
     - **ii.** Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND
       Note: A diagnosis of HAE with normal C1-INH (also referred to as HAE type III) does NOT satisfy this requirement.
     - **iii.** According to the prescriber, the patient has had a favorable clinical response since initiating Orladeyo prophylactic therapy compared with baseline (i.e., prior to initiating prophylactic therapy); AND
       Note: Examples of favorable clinical response include decrease in HAE acute attack frequency, decrease in HAE attack severity, or decrease in duration of HAE attacks.
     - **iv.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Orladeyo is not recommended in the following situations:

35. **Concomitant Use with Other Hereditary Angioedema (HAE) Prophylactic Therapies.** Note: Examples of other HAE prophylactic therapies include Cinryze (C1 esterase inhibitor [human] intravenous infusion), Haegarda (C1 esterase inhibitor [human] subcutaneous injection), and Takhzyro (lanadelumab-flyo subcutaneous injection).
    Orladeyo has not been studied in combination with other prophylactic therapies for HAE, and combination therapy for long-term prophylactic use is not recommended. Patients may use other medications, including Cinryze, for on-demand treatment of acute HAE attacks, and for short-term (procedural) prophylaxis.

36. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Orladeyo® capsules [prescribing information]. Durham, NC: Biocryst; December 2020.
2. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3.
3. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema: the 2021 revision and update. *Allergy*. 2022;77(7):1961-1990.

PRIOR AUTHORIZATION POLICY

POLICY: Hereditary Angioedema – Takhzyro Prior Authorization Policy
- Takhzyro® (lanadelumab-flyo subcutaneous injection – Shire/Takeda)

REVIEW DATE: 09/20/2023

OVERVIEW

Takhzyro, a human monoclonal antibody inhibitor of plasma kallikrein, is indicated for **prophylaxis to prevent attacks of hereditary angioedema (HAE)** in patients ≥ 2 years of age.[1]

Guidelines

According to US HAE Association Medical Advisory Board Guidelines (2020), when HAE is suspected based on clinical presentation, appropriate testing includes measurement of the serum C4 level, C1 esterase inhibitor (C1-INH) antigenic level, and C1-INH functional level.[2] Low C4 plus low C1-INH antigenic or functional level is consistent with a diagnosis of HAE types I/II. The decision on when to use long-term prophylaxis cannot be made on rigid criteria but should reflect the needs of the individual patient. First-line medications for HAE I/II include intravenous C1-INH, Haegarda® (C1-INH [human] subcutaneous injection), or Takhzyro. The guideline was written prior to approval of Orladeyo® (berotralstat capsules).

According to World Allergy Organization/European Academy of Allergy and Clinical Immunology guidelines (2021), it is recommended to evaluate for long-term prophylaxis at every visit, taking disease activity, burden, and control as well as patient preference into consideration.[3] The following therapies are supported as first-line options for long-term prophylaxis: plasma-derived C1-INH (87% agreement), Takhzyro (89% agreement), and Orladeyo (81% agreement). With regard to plasma-derived C1-INH, it is noted that Haegarda provided very good and dose-dependent preventative effects on the occurrence of HAE attacks; the subcutaneous route may provide more convenient administration and maintain improved steady-state plasma concentrations compared with the intravenous route. Of note, androgens are not recommended in the first-line setting for long-term prophylaxis. Recommendations are not made regarding long-term prophylaxis in HAE with normal C1-INH.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Takhzyro. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Takhzyro as well as the monitoring required for adverse events and long-term efficacy, approval requires Takhzyro to be prescribed by or in consultation with a physician who specializes in the condition being treated. A patient who has previously met initial therapy criteria for Takhzyro for the requested indication under the Coverage Review Department and is currently receiving the requested therapy is only required to meet the continuation therapy criteria (i.e., currently receiving Takhzyro). If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Takhzyro, initial therapy criteria must be met.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory records, and prescription claims records.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Takhzyro is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Prophylaxis.** Approve Takhzyro for 1 year if the patient meets one of the following (A or B):
   - **G)** Initial therapy. Approve if the patient meets both of the following (i and ii):
     - **i.** Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
       Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
       - **a)** Patient has low levels of functional C1-INH protein (< 50% of normal) at baseline, as defined by the laboratory reference values **[documentation required]**; AND
       - **b)** Patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values **[documentation required]**; AND
     - **ii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.
   - **H)** Patient is currently receiving Takhzyro prophylaxis. Approve if the patient meets all of the following (i, ii, and iii):
     Note: If the patient is currently receiving the requested therapy, but has not previously received approval of Takhzyro for this indication through the Coverage Review Department, review under criteria for Initial Therapy.
     - **i.** Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND
       Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
     - **ii.** According to the prescriber, the patient has had a favorable clinical response since initiating Takhzyro prophylactic therapy compared with baseline (i.e., prior to initiating prophylactic therapy); AND
       Note: Examples of a favorable clinical response include decrease in HAE acute attack frequency, decrease in HAE attack severity, or decrease in duration of HAE attacks.
     - **iii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Takhzyro is not recommended in the following situations:

37. **Concomitant Use with Other Hereditary Angioedema (HAE) Prophylactic Therapies.** Takhzyro has not been studied in combination with other prophylactic therapies for HAE, and combination therapy for long-term prophylactic use is not recommended. Patients may use other medications, including Cinryze® (C1 esterase inhibitor [human] intravenous infusion), for on-demand treatment of acute HAE attacks, and for short-term (procedural) prophylaxis.
    Note: Examples of other HAE prophylactic therapies include Cinryze (C1 esterase inhibitor [human] intravenous infusion), Haegarda (C1 esterase inhibitor [human] subcutaneous injection), and Orladeyo (berotralstat capsules).

38. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

4. Takhzyro® subcutaneous injection [prescribing information]. Lexington, MA: Takeda; February 2023.
5. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3.
6. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema: the 2021 revision and update. *Allergy*. 2022;77(7):1961-1990.

PRIOR AUTHORIZATION POLICY

POLICY: Homozygous Familial Hypercholesterolemia – Evkeeza Prior Authorization Policy
- Evkeeza® (evinacumab-dgnb intravenous infusion – Regeneron)

REVIEW DATE: 04/26/2023

OVERVIEW

Evkeeza, an angiopoietin-like 3 inhibitor, is indicated as an adjunct to other low-density lipoprotein cholesterol (LDL-C) lowering therapies for the treatment of homozygous familial hypercholesterolemia (HoFH) in patients ≥ 5 years of age.[1]

In the pivotal trial that led to approval of Evkeeza, patients were receiving additional medications to lower LDL-C levels such as statins (94% [77% of patients at high-intensity statin doses]), a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor (77%), ezetimibe (75%), and Juxtapid® (lomitapide capsules). Although some Phase II data are available,[3] the safety and effectiveness of Evkeeza have not been established in patients with other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH).[1] The effects of Evkeeza on cardiovascular (CV) morbidity and mortality have not been determined.

Disease Overview

Familial hypercholesterolemias, which include HeFH and HoFH, encompass a group of genetic defects that cause severe elevations in LDL-C levels, as well as other lipid parameters.[4,5] HoFH impacts approximately 1 in 300,000 to 1,000,000 persons. The condition is most commonly due to impaired functionality of the low-density lipoprotein (LDL) receptor which leads to a low or absence of clearance of LDL-C from the circulation. Currently known causes of familial hypercholesterolemia include mutations in the LDL receptor, apolipoprotein B, or PCSK9 genes. Patients with familial hypercholesterolemia may have physical findings such as tendon or cutaneous xanthomas, which may occur in childhood. Individuals with familial hypercholesterolemia are at very high risk of atherosclerotic cardiovascular disease (ASCVD) at a premature age. Most guidelines recommended LDL-C targets of < 100 mg/dL for adults and < 70 mg/dL for adults with ASCVD or other risk factors. Statins are the initial treatment for familial hypercholesterolemia. For patients with HoFH, high-intensity statin therapy is recommended, with ezetimibe added as well. Therapy with a PCSK9 inhibitor (e.g., Repatha® [evolocumab subcutaneous injection]) is usually the next step. Other non-statin therapies can be considered (e.g., colesevelam tablets or oral suspension, niacin). Combination therapy is required for most patients. LDL apheresis is recommended in certain circumstances. Patients with HoFH should be managed by a lipid specialist. Table 1 provides some of the diagnostic criteria to establish a diagnosis of HoFH. The diagnosis of HoFH can be done by genetic or clinical criteria.

Table 1. Criteria for the Diagnosis of HoFH.[5]

- Genetic confirmation of two mutant alleles at the LDLR, Apo B, PCSK9 or LDLRAP1 gene locus; OR
- An untreated LDL-C > 500 mg/dL* or treated LDL-C ≥ 300 mg/dL* together with either 1) cutaneous or tendon xanthoma before the age of 10 years OR 2) untreated elevated LDL-C levels consistent with heterozygous FH in both parents.

HoFH – Homozygous familial hypercholesterolemia; LDLR – Low-density lipoprotein receptor; Apo B – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9; LDLRAP1 – Low-density lipoprotein receptor adaptor protein 1; LDL-C – Low-density lipoprotein cholesterol; * These cited LDL-C levels are only indicative and lower levels, especially in children or in untreated patients do not exclude HoFH; FH – Familial hypercholesterolemia.

Guidelines

Evkeeza is addressed in the American College of Cardiology Expert Consensus Decision Pathway on the role of non-statin therapies for LDL-C lowering in the management of ASCVD risk (2022).[6] Several guidelines provide strategies for managing familial hypercholesterolemia, including HoFH.[5,7]

- **American College of Cardiology (2022):** Specialized therapies, one of which includes Evkeeza, may be needed to control LDL-C in certain patients (e.g., those with HoFH) who have had an inadequate response to statins, with or without ezetimibe, and PCSK9 inhibitors.[6] Evkeeza should be administered under the care of a lipid specialist.
- **American Heart Association/American College of Cardiology (2018):** In patients with severe primary hypercholesterolemia (LDL-C ≥ 190 mg/dL) begin high-intensity statin therapy.[7] If the LDL-C levels remains ≥ 100 mg/dL, add ezetimibe. If the LDL-C remains ≥ 100 mg/dL on this regimen, consider a PCSK9 inhibitor if the patient has multiple risk factors that increase the risk of ASCVD. Other therapies can also be used (e.g., bile acid sequestrants).
- **European Atherosclerosis Society (2014):** A position paper by this organization recommends lipid-lowering therapy be initiated as soon as possible with LDL-C targets for HoFH of < 100 mg/dL in adults or < 70 mg/dL in adults with clinical ASCVD.[5] Statins are a mainstay of therapy and are often used in combination with other agents such as ezetimibe. Other agents can be alternatives as well (e.g., Juxtapid). Lipoprotein apheresis may also be considered.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Evkeeza. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Evkeeza, as well as the monitoring required for adverse events and long-term efficacy, approval requires Evkeeza to be prescribed by or in consultation with a physician who specializes in the condition being treated. A patient who has previously met Initial Therapy criteria for Evkeeza for the requested indication under the Coverage Review Department and is currently receiving Evkeeza is only required to meet continuation of therapy criteria (i.e., currently receiving therapy). If past criteria has not been met under the Coverage Review Department and the patient is currently receiving Evkeeza, or is restarting Evkeeza, Initial Therapy criteria must be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Evkeeza is recommended in those who meet the following criteria:

FDA-Approved Indication

90. Homozygous Familial Hypercholesterolemia. Approve for 1 year if the patient meets ONE of the following (A or B):

1. Initial Therapy. Approve if the patient meets all of the following (i, ii, iii, iv, and v):

i. Patient is ≥ 5 years of age; AND

ii. Patient meets one of the following (a, b, or c):

a) Patient has had genetic confirmation of two mutant alleles at the low-density lipoprotein receptor (LDLR), apolipoprotein B (apo B), proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene locus; OR

b) Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level > 500 mg/dL AND meets one of the following [(1) or (2)]:
Note: Untreated refers to prior to therapy with any antihyperlipidemic agent.

(1) Patient had clinical manifestations of homozygous familial hypercholesterolemia (HoFH) before the age of 10 years; OR
Note: Clinical manifestations of HoFH are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas, or xanthelasma.

(2) Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia (HeFH); OR
Note: An example of HeFH in both parents would be if both had an untreated LDL-C level ≥ 190 mg/dL and/or an untreated total cholesterol level > 250 mg/dL.

c) Patient has a treated LDL-C level ≥ 300 mg/dL AND meets one of the following [(1) or (2)]:
Note: Treated refers to after therapy with at least one antihyperlipidemic agent. Some examples of antihyperlipidemic agents include statins (e.g., atorvastatin, rosuvastatin, lovastatin, simvastatin, pravastatin), ezetimibe, a PCSK9 inhibitor (i.e., Repatha [evolocumab subcutaneous injection, Praluent [alirocumab subcutaneous injection]), or Juxtapid (lomitapide capsules).

(1) Patient had clinical manifestations of HoFH before the age of 10 years; OR
Note: Examples of clinical manifestations of HoFH are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas, or xanthelasma.

(2) Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with HeFH; AND
Note: An example of HeFH in both parents would be if both had an untreated LDL-C ≥ 190 mg/dL and/or an untreated total cholesterol > 250 mg/dL.

iii. Patient meets one of the following (a or b):

a) Patient meets all of the following [(1), (2), and (3)]:

(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single entity or as a combination product]); AND

(2) Patient has tried one high-intensity statin along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND

(3) Low-density lipoprotein cholesterol level after this treatment regimen remains ≥ 70 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting one of the following [(1) or (2)]:

(1) Patient experienced statin-related rhabdomyolysis; OR
Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]).

(2) Patient meets all of the following [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND
Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

(b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND

(c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND
Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

iv. Patient meets one of the following (a, b, or c):

a) Patient meets both of the following [(1) and (2)]:

(1) Patient has tried one PCSK9 inhibitor for ≥ 8 continuous weeks; AND

Note: Examples of PCSK9 inhibitors include Repatha (evolocumab subcutaneous injection) and Praluent (alirocumab subcutaneous injection).

(2) The LDL-C level after this PCSK9 inhibitor therapy remains ≥ 70 mg/dL; OR

b) Patient is known to have two LDL-receptor negative alleles; OR

c) Patient is 5 to 9 years of age; AND

v. Medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders; OR

2. Patient Currently Receiving Evkeeza. Approve if according to the prescribing physician, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing LDL-C, total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Evkeeza for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Evkeeza, Initial Therapy criteria must be met.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Evkeeza is not recommended in the following situations:

39. HeFH. The safety and effectiveness of Evkeeza have not been established in patients with hypercholesterolemia who do not have HoFH, including those with HeFH.[1]

40. Hyperlipidemia. Although data are available, the prescribing information for Evkeeza states that the safety and efficacy of Evkeeza have not been established in patients with other forms of hypercholesterolemia.[1,3]

Note: This is not associated with HoFH and is referred to as combined hyperlipidemia, hypercholesterolemia (pure, primary), dyslipidemia, or increased/elevated LDL-C levels.

41. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Homozygous Familial Hypercholesterolemia – Juxtapid Prior Authorization Policy
- Juxtapid® (lomitapide capsules – Amryt)

REVIEW DATE: 04/26/2023

OVERVIEW

Juxtapid, a microsomal triglyceride transfer protein inhibitor, is indicated as an adjunct to a low fat diet and other lipid modifying therapies, including low-density lipoprotein (LDL) apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol, apolipoprotein B, and non-high-density lipoprotein cholesterol in adults with **homozygous familial hypercholesterolemia** (HoFH).[1] Limitations of use include that the safety and efficacy of Juxtapid have not been established in patients with hypercholesterolemia who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH).[1] Also, the effect of Juxtapid on cardiovascular (CV) morbidity and mortality have not been determined.

Repatha® (evolocumab subcutaneous [SC] injection) and Praluent® (alirocumab SC injection), two proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors, are indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with HoFH who require additional LDL-C lowering.[2,3] It is notable that patients known to have two LDL-receptor negative alleles (little or no residual function) did not respond or had minimal response to these agents. PCSK9 inhibitors are well tolerated and not associated with hepatotoxicity.[2] Simvastatin, atorvastatin, and rosuvastatin are statins that are indicated for the management of patients with HoFH.[4-6] Ezetimibe is also indicated for use in combination with atorvastatin or simvastatin in patients with HoFH.[7] Ezetimibe/simvastatin tablets are indicated for use in HoFH.[8] Evkeeza® (evinacumab-dgnb intravenous infusion), an angiopoietin-like 3 inhibitor, is also indicated as an adjunct to other LDL-C lowering therapies for the treatment of HoFH in patients ≥ 5 years of age.[9]

Guidelines

- **American College of Cardiology Expert Consensus Decision Pathway on the Role of Non-statin Therapies (2022):** Specialized therapies, one of which includes Juxtapid, may be needed to control LDL-C in certain patients (e.g., those with HoFH) who have had an inadequate response to statins, with or without ezetimibe, and PCSK9 inhibitors.[10] Juxtapid should be administered under the care of a lipid specialist.
- The **2014 HoFH position paper from the Consensus Panel on familial hypercholesterolemia of the European Atherosclerosis Society** states the diagnosis of HoFH is made based on genetic or clinical criteria.[11] A definitive diagnosis can be made by genetic confirmation of two mutant alleles at the low density lipoprotein receptor, apolipoprotein B, PCSK9, or low-density lipoprotein receptor adaptor protein 1 gene locus. However, in some patients genetic confirmation remains elusive. Historically, HoFH has been commonly diagnosed based on LDL-C levels such as an untreated LDL-C > 500 mg/dL, or a treated LDL-C ≥ 300 mg/dL. Also confirming the diagnosis is the presence of xanthomas (cutaneous or tendinous) before 10 years of age or a family of elevated LDL-C levels consistent with HeFH in both parents. Other clinical manifestations of HoFH include arcus cornea or xanthelasma.[11] Initial therapy for HoFH is high-intensity statins; other therapies can be added (e.g., LDL apheresis, Juxtapid).[11-13]

Safety

Juxtapid has a Boxed Warning regarding the risk of hepatotoxicity.[1] Juxtapid may cause elevations in liver transaminases. Also, Juxtapid increases hepatic fat (hepatic steatosis) with or without concomitant increases in transaminases. Due to the risk of hepatotoxicity, Juxtapid is available only through a Risk Mitigation and Strategy Program. Juxtapid is a Pregnancy Category X medication and may cause fetal harm when given to a pregnant woman based on findings suggesting teratogenicity in animals. Females of reproductive potential should obtain a negative pregnancy test before Juxtapid initiation and should utilize effective contraception during Juxtapid use. Juxtapid is associated with gastrointestinal (GI) adverse events (AEs), which occurred in 93% of patients (n = 27/29). GI AEs included diarrhea (79%), nausea (65%), dyspepsia (38%), vomiting (34%), and abdominal pain (34%). Postmarketing reports regarding severe diarrhea have been associated with use of Juxtapid which have involved hospitalization of patients due to diarrhea-related complications such as volume depletion.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Juxtapid. All approvals are provided for the duration noted below. Because of the specialized skills required for managing patients with HoFH, approval requires Juxtapid to be prescribed by or in consultation with a physician who specializes in the condition being treated. A patient who has previously met Initial Therapy criteria for Juxtapid for the requested indication under the Coverage Review Department and is currently receiving Juxtapid is only required to meet continuation of therapy criteria (i.e., currently receiving therapy). If past criteria has not been met under the Coverage Review Department and the patient is currently receiving Juxtapid, or is restarting Juxtapid, Initial Therapy criteria must be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Juxtapid is recommended in those who meet the following criteria:

FDA-Approved Indication

43. Homozygous Familial Hypercholesterolemia (HoFH). Approve for 1 year if the patient meets ONE of the following (A or B):

3. Initial Therapy. Approve if the patient meets all of the following (i, ii, iii, iv, and v):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets one of the following (a, b, or c):

a) Patient has had genetic confirmation of two mutant alleles at the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 gene locus; OR

b) Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level > 500 mg/dL AND meets one of the following [(1) or (2)]:
Note: Untreated refers to prior therapy with any antihyperlipidemic agent.

(1) Patient had clinical manifestation of homozygous familial hypercholesterolemia before 10 years of age; OR
Note: Clinical manifestations of homozygous familial hypercholesterolemia are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas, or xanthelasma.

(2) Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia; OR

Note: An example of heterozygous familial hypercholesterolemia in both parents would be if both had an untreated low-density LDL-C level ≥ 190 mg/dL and/or an untreated total cholesterol level > 250 mg/dL.

c) Patient has a treated LDL-C level ≥ 300 mg/dL AND meets one of the following [(1) or (2)]:

Note: Treated refers to after therapy with at least one antihyperlipidemic agent. Some examples of antihyperlipidemic agents include statins (e.g., atorvastatin, rosuvastatin, lovastatin, simvastatin, pravastatin), ezetimibe, PCSK9 inhibitors (i.e., Repatha [evolocumab subcutaneous injection], Praluent [alirocumab subcutaneous injection]), and Evkeeza (evinacumab-dgnb intravenous infusion).

(1) Patient had clinical manifestations of homozygous familial hypercholesterolemia before 10 years of age; OR

Note: Examples of clinical manifestations of homozygous familial hypercholesterolemia are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma.

(2) Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia; AND

Note: An example of heterozygous familial hypercholesterolemia in both parents would be if both had an untreated LDL-C ≥ 190 mg/dL and/or an untreated total cholesterol > 250 mg/dL.

iii. Patient meets one of the following (a or b):

a) Patient meets both of the following [(1) and (2)]:

(1) Patient has tried at least one proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor for ≥ 8 continuous weeks; AND

Note: Examples of PCSK9 inhibitors include Repatha (evolocumab subcutaneous injection), and Praluent (alirocumab subcutaneous injection).

(2) LDL-C level after this PCSK9 inhibitor therapy remains ≥ 70 mg/dL; OR

b) Patient is known to have two LDL-receptor negative alleles; AND

iv. Patient meets one of the following (a or b):

a) Patient meets all of the following [(1), (2), and (3)]:

(4) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single entity or as a combination product]); AND

(5) Patient has tried one high-intensity statin along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND

(6) Low-density lipoprotein cholesterol level after this treatment regimen remains ≥ 70 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting one of the following [(1) or (2)]:

(1) Patient experienced statin-related rhabdomyolysis; OR

Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]).

(2) Patient meets all of the following criteria [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND

Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

(b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND

(c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND

Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

v. Medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders; OR

4. Patient Currently Receiving Juxtapid. Approve if according to the prescribing physician, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Juxtapid for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Juxtapid, Initial Therapy criteria must be met.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Juxtapid is not recommended in the following situations:

42. Heterozygous Familial Hypercholesterolemia (HeFH). The safety and effectiveness of Juxtapid have not been established in patients with hypercholesterolemia who do not have HoFH, including those with HeFH.[1]

43. Hyperlipidemia. The safety and efficacy of Juxtapid have not been established in patients with hypercholesterolemia who do not have HoFH.[1]

Note: This is not associated with homozygous familial hypercholesterolemia and may be referred to as combined hyperlipidemia, hypercholesterolemia (pure, primary), mixed dyslipidemia, or increased/elevated low-density lipoprotein cholesterol (LDL-C) levels.

44. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Human Immunodeficiency Virus – Apretude Prior Authorization Policy
- Apretude (cabotegravir intramuscular injection – ViiV)

REVIEW DATE: 01/25/2023

OVERVIEW

Apretude, a human immunodeficiency virus-1 (HIV-1) integrase strand transfer inhibitor (INSTI), is indicated in at-risk adults and adolescents weighing ≥ 35 kg for **pre-exposure prophylaxis (PrEP)** to reduce the risk of sexually acquired HIV-1 infection.[1] Individuals must have a negative HIV-1 test prior to initiating Apretude (with or without an oral lead-in with Vocabria® [cabotegravir tablets]) for HIV-1 PrEP. All individuals should be screened for HIV-1 infection prior to each injection of Apretude.

Dosing

Apretude is administered by intramuscular (IM) gluteal injections and must be given by a healthcare provider. Vocabria may be administered for approximately 1 month prior to Apretude (Table 1) or the patient may proceed directly to Apretude without an oral lead-in (Table 2). If an oral lead-in is used, Apretude should be administered on the last day of oral lead-in or within 3 days thereafter (Table 1). Note: Vocabria is only (and will only ever be) available from the manufacturer.

Initial dosing: The recommended initiation dose of Apretude is two, single 600 mg IM injections, given 1 month apart for 2 consecutive months (Months 1 and 2 if no oral lead-in is used [Months 2 and 3 if oral lead-in is used]).[1] After the initiation injection doses, the recommended continuation dose of Apretude is a single 600 mg IM injection every 2 months (Q2M) [starting at Month 4 if no oral-lead in is used or Month 5 if oral lead-in is used]. Apretude may be given up to 7 days before or after the date of the scheduled injection.

Table 1. Recommended Dosing Schedule (with Oral Lead-in) for PrEP.[1]
PrEP – Pre-exposure prophylaxis; IM – Intramuscular; Q2M – Every 2 months; QD – Once daily; [a] Should be administered on the last day of oral lead-in or within 3 days thereafter; [b] Individuals may be given Apretude up to 7 days before or after the date the individual is scheduled to receive the injections.

Table 2. Recommended Dosing Schedule (Direct to Injection) for PrEP.[1]
PrEP – Pre-exposure prophylaxis; IM – Intramuscular; Q2M – Every 2 months; [a] Individuals may be given Apretude up to 7 days before or after the date the individual is scheduled to receive the injections.

Adherence to the injection dosing schedule is strongly recommended. Individuals who miss a scheduled injection visit should be clinically reassessed to ensure resumption of Apretude remains appropriate.

Planned Missed Injections: If an individual plans to miss a scheduled (Q2M) continuation injection visit by > 7 days, take Vocabria 30 mg once daily (QD) for a duration of up to 2 months to replace one missed scheduled (Q2M) injection. The first dose of Vocabria should be taken approximately 2 months after the last injection dose of Apretude. Restart Apretude on the day Vocabria dosing completes or within 3 days (Table 3). For Vocabria durations > 2 months, an alternative oral regimen is recommended.

Unplanned Missed Injections: If a scheduled injection visit is missed or delayed by > 7 days and oral dosing has not been taken in the interim, clinically reassess the individual to determine if resumption of Apretude remains appropriate (if the injection schedule will be continued, see Table 3).

Table 3. Apretude Dosing Recommendations After Missed Injections.[1]
Q2M – Every 2 months

Dose modifications for Apretude are needed when administered with rifabutin. When rifabutin is started before or concomitantly with the first initiation injection of Apretude, the recommended dosing of Apretude is one 600 mg injection, followed 2 weeks later by a second 600 mg initiation injection and monthly thereafter while on rifabutin. When rifabutin is started at the time of the second initiation injection or later, the recommended dosing schedule of Apretude is 600 mg monthly while on rifabutin. After stopping rifabutin, the recommended dosing schedule of Apretude is 600 mg Q2M.

Guidelines

Apretude has been incorporated into the US Public Health Service PrEP for the Prevention of HIV Infection in the US Clinical Practice Guidelines (December 2021).[2] The update was published just prior to the FDA approval of Apretude. A guideline available from the International Antiviral Society-USA (IAS-USA) [December 2022] provides similar guidance to the US Public Health Services guidelines.[3] The World Health Organization (WHO) published a guideline on Apretude for PrEP in 2022 to serve as a supplement to their other oral PrEP recommendations.[4] These guidelines are intended for a broader, world-wide audience, but generally echo the US Public Health Service PrEP and IAS-USA guideline recommendations. Table 4 provides a summary of the recommendations for daily oral PrEP and Apretude (every 2 months).

Table 4. US Public Health Service PrEP Recommendations (December 2021).[2]

Table 4 (continued). US Public Health Service PrEP Recommendations (December 2021). [2]
PrEP – Pre-exposure prophylaxis; [a] Conditioned on FDA-approval at the time of guideline publication; HIV – Human immunodeficiency virus; FTC/TDF – Emtricitabine/tenofovir disoproxil fumarate; IDU – Injection drug user(s); * Individuals assigned male sex at birth whose gender identity is male; † Individuals assigned male sex at birth whose gender identity is female; ‡ Individuals assigned female sex at birth whose gender identity is female.

The US Public Health Service Guidelines also make the following points related to monitoring for PrEP.[2] Prior to prescribing PrEP, acute and chronic HIV infection must be excluded by symptom and HIV testing must be performed immediately before any PrEP regimen is started (IA). Clinicians should document a negative HIV test result within the week before initiating (or reinitiating) PrEP medications, ideally with an antigen/antibody test conducted by a laboratory. The required HIV test prior to initiation of PrEP can be accomplished in one of two ways: 1) drawing blood and sending the specimen to a laboratory for an antigen/antibody test or 2) performing a rapid, point-of-care, FDA-approved, fingerstick antigen/antibody blood test. For PrEP, rapid tests that use oral fluid should not be used to screen for HIV infection because they are less sensitive for the detection of acute or recent infection than blood tests. HIV infection should be assessed every 2 months for patients receiving Apretude so that individuals with incident infection do not continue taking PrEP. When PrEP is prescribed, clinicians should provide access to support for medication adherence and continuation in follow-up PrEP care (IIA) and additional proven effective risk-reduction services to enable the use of PrEP in combination with other effective prevention methods to reduce risk for sexual acquisition of sexually transmitted infections or blood borne bacterial and viral infections though intravenous drug use (IIIA).

Guidelines from the IAS-USA state that for Apretude, HIV testing at initiation and at all visits should ideally include an HIV RNA tests with a lower limit of quantification of ≤ 50 copies/mL AND a laboratory-based antigen-antibody test.[3] If RNA testing is not available, Apretude can still be considered using antigen/antibody screening only. Results of such testing do not need to be available to provide injections.

The WHO guidelines for Aptretude in PrEP enforce that HIV testing prior to offering Apretude is required and should be continued prior to each injection with Apretude.[4] Only individuals who are HIV-negative should be initiated on PrEP. HIV testing can be conducted using quality-assured serology assays (i.e., rapid diagnostic tests and enzyme immunoassays).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Apretude. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Apretude as well as the monitoring required for adverse events and long-term efficacy, approval requires Apretude to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Apretude is recommended in those who meet the following criteria:

FDA-Approved Indication

91. Pre-exposure Prophylaxis (PrEP) of Human Immunodeficiency Virus (HIV)-1 Infection. Approve for 2 months if the patient meets the following criteria (A, B, C, and D):

A) Patient is ≥ 35 kg; AND
B) Patient meets both of the following conditions (i and ii):
  i. The medication will be administered only if the patient has a negative HIV-1 test result ≤ 1 week prior to the dose of Apretude; AND
  ii. The medication will be administered only if the patient has no signs or symptoms of acute HIV infection, according to the prescriber: AND
C) The medication is prescribed as part of a comprehensive HIV-1 prevention strategy (i.e., adherence to administration schedule and safer sex practices, including condoms); AND
D) The medication is prescribed by or in consultation with a physician who specializes in the treatment of HIV infection.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Apretude is not recommended in the following situations:

141. Treatment of Human Immunodeficiency Virus (HIV). Apretude is not indicated for the treatment of HIV. It is inadequate therapy for established HIV infection and use in persons with early HIV infection may encourage resistance of one or more of the PrEP medications.[2]

142. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Human Immunodeficiency Virus – Cabenuva Prior Authorization Policy
- Cabenuva® (cabotegravir extended-release intramuscular injection; rilpivirine extended-release intramuscular injection, co-packaged – ViiV/GlaxoSmithKline)

REVIEW DATE: 02/01/2023; selected revision 12/06/2023

OVERVIEW

Cabenuva is a two-drug co-packaged product of cabotegravir, a human immunodeficiency virus type-1 (HIV-1) integrase strand-transfer inhibitor, and rilpivirine, an HIV-1 non-nucleoside reverse transcriptase inhibitor.[1] It is indicated as a complete regimen for the treatment of **HIV-1 infection** in patients ≥ 12 years of age and weighing ≥ 35 kg to replace their current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to cabotegravir or rilpivirine.

Dosing

Cabenuva must be administered by a healthcare professional. Prior to starting Cabenuva, healthcare professionals should carefully select patients who agree to the required monthly injection dosing schedule and counsel patients about the importance of adherence to scheduled dosing visits to help maintain viral suppression and reduce the risk of viral rebound and potential development of resistance with missed doses.[1]

Oral lead-in with Vocabria® (cabotegravir tablets) + Edurant® (rilpivirine tablets) may be used for approximately 1 month (at least 28 days) prior to the initiation of Cabenuva to assess the tolerability of cabotegravir and rilpivirine. Cabenuva may be administered as a once-monthly injection or once every 2-month injection. Table 1 provides the recommended oral lead-in and monthly injection dosing schedule. Table 2 provides the recommended oral lead-in and every 2-month injection dosing schedule.

Table 1. Recommended Oral Lead-In and Monthly Intramuscular Injection Dosing Schedule.[1]
QD – Once daily.

Table 2. Recommended Oral Lead-In and Every 2-Month Intramuscular Injection Dosing Schedule.[1]
QD – Once daily.

Guidelines

The Department of Health and Human Services (DHHS) Guidelines for the Use of Antiviral Agents in Adults and Adolescents with HIV (September 21, 2022) recognize Cabenuva as a long-acting antiretroviral regimen that is an optimization option for patients who are engaged with their health care providers, virologically suppressed on oral therapy for 3 to 6 months, and who agree to make the frequent clinic visits needed.[5] Both FDA-approved dosing regimens are appropriate for Cabenuva in virally suppressed patients (once monthly or every 2-month dosing and with or without oral lead-in). The Guidelines point out that the tablet formulation of cabotegravir (Vocabria®) is only available through the manufacturer, not in community pharmacies. Cabenuva is not recommended as initial therapy for people with HIV because of the lack of data supporting efficacy in this patient population.

International Antiviral Society-USA (IAS-USA) Recommendations on Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults (2022) have similar recommendations to the DHHS guidelines for Cabenuva.[7] In individuals with no of treatment failure and no known or suspected resistance to either agent, Cabenuva is an option. Cabenuva is noted to give greater patient satisfaction (vs. oral antiretrovirals

(ARVs) to those interested in non-oral options for treatment because of privacy, stigma, or convenience reasons. Both approved dosing regimens (with and without oral lead-in) are considered acceptable based on patient preference. If scheduled doses of Cabenuva are missed, resumption of therapy should follow the Prescribing Information. Cabenuva is not recommended for initial therapy in ARV-naïve individuals.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cabenuva. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cabenuva as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Cabenuva to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Cabenuva as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cabenuva is recommended in those who meet the following criteria:

FDA-Approved Indication

92. Human Immunodeficiency Virus (HIV)-1, Treatment. Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets all of the following (i, ii, iii, iv, and v):
- **i.** Patient is ≥ 12 years of age; AND
- **ii.** Patient weighs ≥ 35 kg; AND
- **iii.** Patient has HIV-1 RNA < 50 copies/mL (viral suppression) **[documentation required]**; AND
- **iv.** Prior to initiating Cabenuva or 1 month lead-in with Vocabria (cabotegravir tablets), the patient was treated with a stable regimen (≥ 4 months) of antiretrovirals for HIV-1 **[documentation required]**; AND
- **v.** The medication is prescribed by or in consultation with a physician who specializes in the treatment of HIV infection.

B) Patient is Currently Receiving Cabenuva. Approve if the patient has HIV-1 RNA < 50 copies/mL (viral suppression) **[documentation required]**.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cabenuva is not recommended in the following situations:

143. Pre-Exposure Prophylaxis (PrEP) of Human Immunodeficiency Virus (HIV)-1 Infection. Cabenuva is not indicated for the prevention of HIV.

144. Co-administration with Antiretrovirals for Human Immunodeficiency Virus (HIV) Treatment. Because Cabenuva is a complete regimen, co-administration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended.[1]

145. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Human Immunodeficiency Virus – Rukobia Prior Authorization Policy
- Rukobia™ (fostemsavir extended-release tablets – ViiV/GlaxoSmithKline)

REVIEW DATE: 07/12/2023

OVERVIEW

Rukobia is a human immunodeficiency virus type-1 (HIV-1) gp120-directed attachment inhibitor.[1] It is indicated in combination with other antiretroviral(s) [ARVs] for the treatment of HIV-1 infection in heavily treatment-experienced adults with **multidrug-resistant HIV-1 infection** failing their current ARV regimen due to resistance, intolerance, or safety considerations.

Clinical Efficacy

The efficacy of Rukobia was established in one ongoing, Phase III, multicenter, 96-week pivotal study in heavily treatment-experienced adults with HIV-1 infection failing their current ARV regimen (BRIGHTE; n = 371).[2,5] Eligible patients were ≥ 18 years of age and had failure of their current ARV regimen (baseline HIV-1 RNA ≥ 400 copies/mL), with no viable ARV combination therapy available because of exhaustion of a least four of six ARV classes (i.e., nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, integrase inhibitors, protease inhibitors, CCR5 antagonists, and entry inhibitors). Exhaustion was defined as the elimination of all ARVs within a given class as a fully active option to pair with Rukobia because of resistance, previous adverse events, or unwillingness to use Fuzeon® (enfuviritide subcutaneous injection). There were 15 patients who received Trogarzo® (ibalizumab-uiyk intravenous injection) in combination with Rukobia.

Guidelines

According to the Department of Health and Human Services Guidelines (May 26, 2023) for the use of antiviral agents in adults and adolescents with HIV infection, treatment-experienced patients with ongoing detectable viremia who lack sufficient treatment options to construct a fully suppressive regimen may be candidates for Trogarzo, Rukobia, or Sunlenca® (lenacapavir tablets/subcutaneous injection).[3] Patients who continue to have detectable viremia and who lack sufficient treatment options to construct a fully suppressive regimen may also be candidates for research studies or expanded access programs, or they may qualify for single-patient access to an investigational new drug as specified in FDA regulations. The International Antiviral Society-USA recommendations (2022) for the treatment and prevention of HIV in adults recognize Rukobia in the setting of integrase strand-transfer inhibitor (INSTI) resistance. If INSTI resistance is relatively limited and a new antiviral regimen is to include an INSTI, the regimen should also include at least one and preferably two other fully active drugs, optimally from drug classes not previously used which may include among other agents, Rukobia.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Rukobia. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Rukobia as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Rukobia to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rukobia is recommended in those who meet the following criteria:

FDA-Approved Indication

93. Human Immunodeficiency Virus (HIV) Infection. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, and vi):

i. Patient is ≥ 18 years of age; AND

ii. Patient has HIV type 1 (HIV-1) infection; AND

iii. According to the prescriber, the patient is failing a current antiretroviral regimen for HIV; AND

iv. According to the prescriber, the patient has exhausted at least FOUR of the following antiretroviral classes defined as elimination of all antiretrovirals within a given class due to demonstrated or projected resistance to the agent(s) in that class OR due to significant intolerance (FOUR of a, b, c, d, e, or f):

a) Nucleoside reverse transcriptase inhibitor; OR

Note: Examples of nucleoside reverse transcriptase inhibitors include abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir disoproxil fumarate, tenofovir alafenamide, zidovudine.

b) Non-nucleoside reverse transcriptase inhibitor; OR

Note: Examples of non-nucleoside reverse transcriptase inhibitor include delaviridine, efavirenz, etravirine, nevirapine, nevirapine XR, rilpivirine.

c) Protease inhibitor; OR

Note: Examples of protease inhibitors include atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, tipranavir.

d) Fusion inhibitor; OR

Note: Examples of fusion inhibitors include Fuzeon (enfuviritide subcutaneous injection).

e) Integrase strand transfer inhibitor; OR

Note: Examples of integrase strand transfer inhibitors include raltegravir, dolutegravir, elvitegravir.

f) CCR5 antagonist; AND

Note: Examples of CCR5 antagonists include Selzentry (maraviroc tablets).

v. The medication will be taken in combination with an optimized antiviral background regimen including one or more other antiretroviral agents; AND

vi. The medication is prescribed by or in consultation with a physician who specializes in the treatment of HIV infection.

B) Patient is Currently Receiving Rukobia. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has HIV-1 infection; AND

ii. The medication will continue to be taken in combination with an optimized antiviral background regimen including one or more other antiretroviral agents; AND

iii. Patient has responded to a Rukobia-containing regimen, as determined by the prescriber.
Note: Examples of a response are HIV RNA < 40 cells/mm^3, HIV-1 RNA ≥ 0.5 $\log_{10}$ reduction from baseline in viral load.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rukobia is not recommended in the following situations:

146. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Human Immunodeficiency Virus – Sunlenca Prior Authorization Policy
- Sunlenca® (lenacapavir tablets and subcutaneous injection – Gilead)

REVIEW DATE: 01/03/2024

OVERVIEW

Sunlenca, a human immunodeficiency virus type 1 (HIV-1) capsid inhibitor, is indicated in combination with other antiretroviral(s) for the treatment of **multidrug resistant HIV-1 infection** in heavily treatment-experienced adults failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.[1]

Clinical Efficacy

The efficacy of Sunlenca was evaluated in one Phase II/III, randomized, double-blind, placebo-controlled, multicenter, pivotal study in patients with multidrug resistant HIV-1.[2] Eligible patients had documented resistance to two or more agents from three of four main antiretroviral classes (nucleoside reverse transcriptase inhibitor [NRTI], non-nucleoside reverse transcriptase inhibitor [NNRTI], protease inhibitor, and integrase strand-transfer inhibitor [INSTI]) and two or fewer active antiretrovirals from the four main classes that could be effectively combined for optimized background therapy.

Guidelines

According to the Department of Health and Human Services Guidelines for the use of antiretrovirals in adults and adolescents with HIV (December 6, 2023), in patients with multidrug resistance without fully active antiretroviral options, consensus on optimal management is lacking.[4] Maximal virologic suppression remains the goal of treatment; however, if it cannot be achieved, the goals are to preserve immune function, prevention clinical progression, and minimize the development of further resistance that may compromise future regimens. The Guidelines note that that even partial virologic suppression of HIV-1 RNA to > 0.5 $\log_{10}$ copies/mL from baseline correlates with clinical benefit. There is evidence that continuing antiretroviral therapy even in the presence of viremia and the absence of CD4+ count increases, reduces the risk of disease progression. Additional data suggest that even modest reductions in HIV-1 RNA levels continue to confer immunologic and clinical benefits. In general, adding a single, fully active antiretroviral to the regimen is not recommended because of the risk of rapid development of resistance. Patients with ongoing detectable viremia who lack sufficient treatment options to construct a fully suppressive regimen are noted to be candidates for Rukobia™ (fostemsavir extended-release tablets), Sunlenca, and/or Trogarzo® (ibalizumab-uiyk intravenous infusion). For people with multidrug-resistant HIV-2, Trogarzo and Sunlenca may be considered based on *in vitro* data. Optimal treatment strategies for individuals with HIV-2 are not defined.

The International Antiviral Society-USA (December 2022) provides some guidance on patients with viral failure; Sunlenca is mentioned in patients with INSTI resistance as a product under FDA review.[5] Management of INSTI resistance can be difficult and guidance from an expert in HIV drug resistance is recommended for selection of the optimal regimen. If INSTI resistance is relatively limited, and a new regimen is to include an INSTI, dolutegravir should be administered twice daily. The regimen should also include at least one, and preferably two other fully active drugs, optimally from drug classes not previously used. Therapies may include Rukobia, Sunlenca (currently under FDA review), Selzentry® (maraviroc tablets, generic and oral solution), Trogarzo, or Fuzeon® (enfuviritide SC injection).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Sunlenca. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sunlenca as well as the monitoring required for adverse events and long-term efficacy, approval requires Sunlenca to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Sunlenca is recommended in those who meet the following criteria:

FDA-Approved Indication

94. Human Immunodeficiency Virus (HIV)-1 Infection, Treatment. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, and v):

iv. Patient is ≥ 18 years of age; AND

v. According to the prescriber, the patient is failing a current antiretroviral regimen for HIV; AND

iii. According to the prescriber, the patient has resistance to two or more agents from at least THREE of the following antiviral classes (a, b, c, d):

a) Nucleoside reverse transcriptase inhibitor;

Note: Examples of nucleoside reverse transcriptase inhibitors include abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir disoproxil fumarate, tenofovir alafenamide, zidovudine.

b) Non-nucleoside reverse transcriptase inhibitor;

Note: Examples of non-nucleoside reverse transcriptase inhibitors include delaviridine, efavirenz, etravirine, nevirapine, nevirapine XR, rilpivirine.

c) Protease inhibitor;

Note: Examples of protease inhibitors include atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, tipranavir.

d) Integrase strand transfer inhibitor; AND

Note: Examples of integrase strand transfer inhibitors include raltegravir, dolutegravir, elvitegravir.

iv. The medication will be taken in combination with an optimized antiviral background regimen including one or more other antiretroviral agents; AND

v. The medication is prescribed by or in consultation with a physician who specializes in the treatment of HIV infection.

C) Patient is Currently Receiving Sunlenca. Approve for 1 year if the patient meets BOTH of the following (i and ii):

iv. The medication will continue to be taken in combination with an optimized antiviral background regimen including one or more other antiretroviral agents; AND

v. Patient has responded to a Sunlenca-containing regimen, as determined by the prescriber.
Note: Examples of a response are HIV RNA < 50 cells/mm^3, HIV-1 RNA ≥ 0.5 $\log_{10}$ reduction from baseline in viral load.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Sunlenca is not recommended in the following situations:

147. Pre-Exposure Prophylaxis (PrEP) of Human Immunodeficiency Virus (HIV). Sunlenca is not approved for this indication; however, it is under investigation in two Phase III, unpublished, and ongoing clinical trials for PrEP (PURPOSE 1 and PURPOSE 2).[7,8]

148. Human Immunodeficiency Virus (HIV), Treatment in Treatment-Naïve Patients. Sunlenca is not approved for this indication; however, it is under investigation in one Phase II ongoing clinical trial in treatment-naïve adults with HIV-1 (CALIBRATE).[3]

149. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Human Immunodeficiency Virus – Trogarzo Prior Authorization Policy
- Trogarzo® (ibalizumab-uiyk intravenous injection – Theratechnologies)

REVIEW DATE: 03/29/2022

OVERVIEW

Trogarzo is a long-acting humanized immunoglobulin G4 monoclonal antibody indicated in combination with other antiretroviral(s) for the treatment of **human immunodeficiency virus type-1 (HIV-1) infection** in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen.[1] Patients should receive a single intravenous loading dose of 2,000 mg followed by a maintenance dose of 800 mg once every 2 weeks. Maintenance doses of Trogarzo can be administered as a diluted intravenous (IV) infusion or undiluted IV push.

Disease Overview

Multiclass or three-class drug resistant HIV-1 infection is usually defined as the presence of phenotypic or genotypic resistance to resistance to at least one drug in each of the following three classes: the nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors classes.[2] Trogarzo blocks HIV-1 from infecting CD4+ T cells by binding to domain 2 of CD4.[1] This interferes with post-attachment steps required for the entry of HIV-1 virus particles into host cells and prevents the viral transmission that occurs via cell-cell fusion. The binding specificity to domain 2 of CD4 allows Trogarzo to block viral entry into host cells without causing immunosuppression. There is no antagonism with other antiretrovirals. In the pivotal trial for Trogarzo, all patients had documented resistance to at least one antiretroviral from the nucleoside reverse transcriptase inhibitor, non-nucleoside reverse transcriptase inhibitor, and protease inhibitor classes.

Guidelines

The Department of Health and Human Services guidelines for the treatment of adults and adolescents with HIV-1 recognize the difficulty in treating patients with extensive resistance.[3] Managing patients with extensive resistance is complex and usually requires consultation with an HIV expert. Patients with ongoing detectable viremia who lack sufficient treatment options to construct a fully suppressive regimen may be candidates for Trogarzo.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Trogarzo. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Trogarzo as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Trogarzo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Trogarzo is recommended in those who meet the following criteria:

FDA-Approved Indication

95. Human Immunodeficiency Virus (HIV)-1 Infection. Approve for the duration outlined below if the patient meets the following criteria (A and B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following conditions (i, ii, iii, iv, and v):

i. Patient is ≥ 18 years of age; AND

ii. According to the prescriber, the patient is failing a current antiretroviral regimen for HIV; AND

iii. Patient has multiple antiretroviral drug resistance as demonstrated by resistance to at least one antiretroviral from at least THREE of the following antiviral classes (a, b, c, d, e, f):

a) Nucleoside reverse transcriptase inhibitor
Note: Examples of nucleoside reverse transcriptase inhibitors include but are not limited to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir disoproxil fumarate, tenofovir alafenamide, zidovudine.

b) Non-nucleoside reverse transcriptase inhibitor;
Note: Examples of non-nucleoside reverse transcriptase inhibitors include but are not limited to delavirdine, efavirenz, etravirine, nevirapine, nevirapine XR, rilpivirine.

c) Protease inhibitor;
Note: Examples of protease inhibitors include but are not limited to atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, tipranavir.

d) Fusion inhibitor;
Note: An example of a fusion inhibitor includes but is not limited to Fuzeon (enfuviritide for injection).

e) Integrase strand transfer inhibitor;
Note: Examples of integrase strand transfer inhibitors include but are not limited to raltegravir, dolutegravir, and elvitegravir.

f) CCR5-antagonist; AND
Note: An example of a CCR5-antagonist includes but is not limited to Selzentry (maraviroc tablets).

iv. The medication will be taken in combination with an optimized antiviral background regimen including one or more other antiretroviral agents; AND

v. The medication is prescribed by or in consultation with a physician who specializes in the treatment of HIV infection.

B) Patient is Currently Receiving Trogarzo. Approve for 1 year if the patient meets ALL of the following conditions (i and ii):

i. The medication will continue to be taken in combination with an optimized antiviral background regimen including one or more other antiretroviral agents; AND

ii. Patient has responded (e.g., HIV-1 RNA ≥ 0.5 $\log_{10}$ reduction from baseline in viral load) to a Trogarzo-containing regimen, as determined by the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Trogarzo is not recommended in the following situations:

150. Human Immunodeficiency Virus (HIV)-2. Trogarzo has only been evaluated in HIV-1 infection. The Department of Health and Human Services guidelines for the treatment of adults and adolescents with HIV-1 state that there are no data on the activity of Trogarzo against HIV-2.[3]

151. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Hyaluronic Acid Derivatives (Intraarticular) Prior Authorization Policy

- Durolane® (sodium hyaluronate injection – Bioventus)
- Euflexxa® (sodium hyaluronate injection – Ferring)
- Gel-One® (sodium hyaluronate injection – Seikagaku/Zimmer)
- Gelsyn-3™ (sodium hyaluronate injection – Bioventus)
- GenVisc® 850 (sodium hyaluronate injection – OrthogenRx)
- Hyalgan® (sodium hyaluronate injection – Fidia)
- Hymovis® (high molecular weight viscoelastic hyaluronan injection – Fidia)
- Monovisc™ (high molecular weight hyaluronan injection – Anika)
- Orthovisc® (high molecular weight hyaluronan injection – Anika)
- Supartz FX™ (sodium hyaluronate injection – Seikagaku/Bioventus)
- Sodium hyaluronate 1% injection – Teva
- SynoJoynt™ (sodium hyaluronate injection – Arthrex)
- Synvisc® (hylan G-F 20 sodium hyaluronate injection – Genzyme)
- Synvisc-One® (hylan G-F 20 sodium hyaluronate injection – Genzyme)
- Triluron™ (sodium hyaluronate injection – Fidia)
- TriVisc™ (sodium hyaluronate injection – OrthogenRx)
- Visco-3™ (sodium hyaluronate injection – Seikagaku/Bioventus)

REVIEW DATE: 09/27/2023

OVERVIEW

Hyaluronic acid derivatives are indicated for the treatment of **pain related to knee osteoarthritis** in patients who have failed to respond adequately to conservative nonpharmacologic therapy and to simple analgesics (e.g., acetaminophen).[1-16,43] The use of intraarticular injections are to restore the normal properties (viscosity and elasticity) of the synovial fluid. Gel-One, Hyalgan, Supartz FX, Synvisc/Synvisc-One, Triluron, and Visco-3 are derived from rooster or chicken combs. The remaining products are derived from non-avian sources and may be useful for patients with allergies to eggs or poultry products. GenVisc 850 has data to support similarity to Supartz FX.[9] Although retreatment data are limited, all of these products have data concerning efficacy and/or safety of repeat courses. In many cases, at least 6 months was required or a minimum of 6 months had elapsed prior to injection of a repeat course.

Guidelines

Guidelines for the medical management of osteoarthritis of the hand, hip, and knee are available from the American College of Rheumatology (2019).[17] Multiple non-pharmacological modalities are recommended for knee osteoarthritis, including exercise, self-management programs, weight loss, Tai Chi, and use of assistive devices (i.e., bracing or a cane). Pharmacologic therapy for knee osteoarthritis consists of acetaminophen, oral and topical non-steroidal anti-inflammatory drugs (NSAIDs), tramadol, intraarticular corticosteroid injections, duloxetine, and topical capsaicin. There is limited evidence establishing a benefit of hyaluronic acid intraarticular injections, which contributes to the conditional recommendation against use in knee osteoarthritis. However, when other alternatives have been exhausted or have failed to provide satisfactory benefit, use of intraarticular hyaluronic acid injections may be viewed more favorably than offering no intervention. In the guidelines, no distinction is made between the available intraarticular hyaluronic acid products or between products with various molecular weights.

The Osteoarthritis Research Society International also has guidelines for knee osteoarthritis (2019).[19] These guidelines note that use of intraarticular hyaluronic acid injections are conditionally recommended for

patients with knee osteoarthritis. The guidelines comment on the long-term treatment effect with intraarticular hyaluronic acid injections which is associated with symptom improvement beyond 12 weeks and a more favorable safety profile than intraarticular corticosteroid injections.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of hyaluronic acid derivatives indicated for knee osteoarthritis. Because of the specialized skills required for evaluation and diagnosis of patients treated with hyaluronic acid derivative intraarticular products as well as the specialized administration technique, these products are required to be administered by or under the supervision of a physician specializing in rheumatology, orthopedic surgery, or physical medicine and rehabilitation (physiatrist). All approvals are provided for one course of therapy per treated knee. Note that 1 month is a sufficient approval duration for one course of Durolane, Euflexxa, Gel-One, Gelsyn-3, Hymovis, Monovisc, sodium hyaluronate 1% injection, SynoJoynt, Synvisc, Synvisc-One, Triluron, TriVisc, and Visco-3; 5 weeks is a sufficient approval duration for one course of GenVisc 850, Orthovisc, Hyalgan, and Supartz FX. Previous therapy is required to be verified by a clinician in the Coverage Review Department when noted in the criteria as **[verification of therapies required]**.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of hyaluronic acid derivatives is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Osteoarthritis of the Knee.** Approve one course of therapy per treated knee if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve an initial course if the patient meets ALL of the following (i, ii, and iii):
   - **i.** Diagnosis of the knee to be treated is confirmed by radiologic evidence of knee osteoarthritis; AND
     Note: Examples of radiographic evidence includes x-ray, magnetic resonance imaging (MRI), computed tomography (CT) scan, ultrasound.
   - **ii.** Patient has tried at least TWO of the following three modalities of therapy for osteoarthritis (a, b, c):
     - **a)** At least one course of physical therapy for knee osteoarthritis;
     - **b)** At least TWO of the following pharmacologic therapies [(1), (2), (3), (4)] **[verification of therapies required]**:
       - **(1)** Oral or topical nonsteroidal anti-inflammatory drug(s) [NSAID(s)];
         Note: Examples of oral NSAIDs include naproxen, ibuprofen, celecoxib. Examples of topical NSAIDs include diclofenac solution or diclofenac gel. A trial of two or more NSAIDs (oral and/or topical) counts as one pharmacologic therapy.
       - **(2)** Acetaminophen;
       - **(3)** Tramadol (Ultram/XR, generic);
       - **(4)** Duloxetine (Cymbalta, generic);
     - **c)** At least TWO injections of intraarticular corticosteroids to the affected knee; AND
   - **iii.** The product is administered by or under the supervision of a physician specializing in rheumatology, orthopedic surgery, or physical medicine and rehabilitation (physiatrist).

B) Patient has Already Received One or More Courses of Hyaluronic Acid Derivative in the Same Knee. Approve ONE repeat course if the patient meets ALL of the following (i, ii, and iii)

i. At least 6 months have elapsed since the last injection with any hyaluronic acid derivative; AND

ii. According to the prescriber, the patient had a response to the previous course of hyaluronic acid derivative therapy for osteoarthritis of the knee and now requires additional therapy for osteoarthritis symptoms; AND
Note: Examples of a response include reduced joint pain, tenderness, morning stiffness, or improved mobility.

iii. The product is administered by or under the supervision of a physician specializing in rheumatology, orthopedic surgery, or physical medicine and rehabilitation (physiatrist).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of hyaluronic acid derivatives is not recommended in the following situations:

18. Acute Ankle Sprain. A randomized, controlled, prospective trial was conducted which assessed the use of intraarticular hyaluronic acid in acute ankle sprains.[20-21] Patients treated with intraarticular hyaluronic acid (n = 79) within 48 hours of injury and again on Day 4 reported a time to pain-free and disability-free return to sport of 11 days (± 8 days) compared with 17 days (± 8 days) for placebo ($P < 0.05$). All patients were also treated with standard of care (rest, ice, compression, and elevation). At 24 months, the placebo group experienced an increase in repeat sprains when compared with those treated with an intraarticular hyaluronic acid product (21 recurrent ankle sprains in the placebo group compared with 7 recurrent ankle sprains in the intraarticular hyaluronic acid treatment group [$P < 0.001$]) as well as a significant difference in missed days from participation in sport activity (49 days vs. 12 days for the placebo and hyaluronic acid groups, respectively; $P < 0.001$).[21] More data are needed to determine the role of intraarticular hyaluronic acid products in the treatment of acute ankle sprains.

37.

19. **Osteoarthritis and Other Pathologic Conditions Involving Joints Other than the Knee** (e.g., hand, hip, ankle, shoulder osteoarthritis, temporomandibular joint [TMJ], adhesive capsulitis of the shoulder, subacromial impingement). The prescribing information for these agents state in the precautions section that the safety and effectiveness of hyaluronic acid derivatives injections into joints other than the knee have not been established.[1-16] Due to the absence of evidence to support use of intraarticular hyaluronic acid and potential for harm, the guidelines for the management of hand, hip, and knee osteoarthritis by American College of Rheumatology (2019) do not recommend use of intraarticular hyaluronic acid in patients with hand or hip osteoarthritis.[17] Small trials have also investigated intraarticular hyaluronic acid in other joints, including ankle osteoarthritis and hip osteoarthritis.[23-38] More data are needed to determine if there is a role for intraarticular hyaluronic acid for the treatment of osteoarthritis involving other joints. A small trial (n = 70) found that intraarticular hyaluronic acid did not result in increased benefit for adhesive capsulitis of the shoulder (also known as frozen shoulder) in patients who were already receiving physical therapy.[39] Another small study (n = 159) did not show benefit of intraarticular hyaluronic acid over corticosteroid or placebo injections in patients with subacromial impingement.[40]

Pathologic Conditions of the Knee Other than Osteoarthritis (e.g., chondromalacia patellae, osteochondritis dissecans, patellofemoral syndrome, post-anterior cruciate ligament [ACL] reconstruction). Intraarticular hyaluronic acid products are indicated in knee osteoarthritis.[1-16] Adequate, well-designed trials have not clearly established the use of intraarticular hyaluronic acid in other conditions of the knee.[41-42]

20. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Hyperlipidemia – Nexletol Prior Authorization Policy
- Nexletol® (bempedoic acid tablets – Esperion)

REVIEW DATE: 04/26/2023; selected revision 05/03/2023

OVERVIEW

Nexletol, an adenosine triphosphate-citrate lyase inhibitor, is indicated as an adjunct to diet and statin therapy for the treatment of primary hyperlipidemia in adults with the following:[1]

- **Atherosclerotic cardiovascular disease (ASCVD)** for those who require additional lowering of low-density lipoprotein cholesterol (LDL-C).
- **Heterozygous familial hypercholesterolemia** (HeFH) for those who require additional lowering of LDL-C.

The safety and effectiveness have not been established in pediatric patients.[1]

Clinical Efficacy

CLEAR Outcomes was a randomized, double-blind, placebo-controlled trial involving 13,970 adults, 18 to 85 years of age who were unable or unwilling to take statins due to unacceptable adverse events among those who had, or were at high risk for, CV disease.[2] Those eligible had to report being statin intolerant. Patients were assigned to receive Nexletol or placebo. Use of statins at very low doses were permitted, as well as other lipid lowering therapies (e.g., ezetimibe, bile acid sequestrants, fibrates). The mean patient age was 65 years. In total, 70% of patients had a previous CV event (secondary prevention population) whereas 30% of patients were categorized as being in the primary prevention group. At baseline, 22.7% of patients were utilizing a statin and 11.5% were on ezetimibe. The mean LDL-C at baseline was 139 mg/dL. The median follow-up was 40.6 months. The mean LDL-C level after 6 months of treatment with Nexletol was 107 mg/dL for the Nexletol group vs. 136 mg/dL for placebo. The primary endpoint (death from CV causes, nonfatal myocardial infarction [MI], nonfatal stroke, or coronary revascularization) occurred in 11.7% of patients in the Nexletol group vs. 13.3% in the placebo group (P = 0.004). The composite of death from CV causes, nonfatal stroke, or nonfatal MI occurred in 8.2% of patients given Nexletol vs. 9.5% of patients in the placebo group (P = 0.006).

Guidelines

Many guidelines are available regarding the treatment of patients with dyslipidemia which include the management of HeFH and ASCVD.[3-10] For patients with elevated LDL-C, statins are the cornerstone of therapy and recommended first-line to be used at maximally tolerated doses due to the established benefits regarding the reduction of CV risks. Atorvastatin 40 mg to 80 mg once daily (QD) and rosuvastatin 20 mg to 40 mg QD are considered high-intensity statins as they achieve LDL-C lowering of ≥ 50%.

- The **American College of Cardiology Expert Consensus Decision Pathway on the Role of Non-Statin Therapies** for LDL-Cholesterol Lowering in the Management of ASCVD Risk (2022) make several recommendations; Nexletol is addressed.[3] For adults with clinical ASCVD at very high risk (e.g., patients with major ASCVD events, HeFH, diabetes) who are on statin therapy for secondary prevention, the general goal is ≥ 50% LDL-C reduction and an LDL-C < 55 mg/dL (of non-HDL-C < 85 mg/dL) with maximally tolerated statin therapy. If the above goals are not achieved, the initial non-statin agents recommended include ezetimibe and/or a proprotein convertase subtilisin kexin type 9 (PCSK9) monoclonal antibody (i.e., Repatha or Praluent). Nexletol can be considered after these therapies.

- The **American Association of Clinical Endocrinologists and American College of Endocrinology** has guidelines regarding the management of dyslipidemia and the prevention of CV disease (2020).[7] Nexletol is mentioned is cited as an option for intensification of therapy after use of standard agents such as high-intensity/moderate-intensity statins.
- The **International Lipid Expert Panel** published a position paper in 2023 on use of Nexletol in the management of lipid disorders and CV risk.[10] One recommendation is that in patients with statin intolerance, Nexletol monotherapy, or in combination with ezetimibe and other non-statin drugs is recommended to enable patients to achieve therapeutic goals. In primary prevention, Nexletol may be considered for patients at high and very high CV risk who despite optimally maximally tolerated doses of statins and ezetimibe, are not achieving target LDL-C levels.
- The **American Heart Association (AHA)/American College of Cardiology** guidelines on the management of blood cholesterol (2018) define ACSVD as acute coronary syndrome, those with a history of MI, stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack, or peripheral arterial disease.[4,5] An LDL-C < 70 mg/dL is recommended for most patients with ASCVD to reduce CV risk. Guidelines and reviews have recognize that patients with an elevated coronary artery calcium or calcification score (e.g., ≥ 300 Agatston units) are at an increased risk of CV events.[8,11-14]
- **The AHA** published a scientific statement regarding familial hypercholesterolemia (2015).[9] Key points are that the condition may start early (in childhood or adolescence) and is noted by LDL-C levels ≥ 190 mg/dL. Premature CV disease can result. Diagnosis can be confirmed by genetic testing. The Dutch Lipid Clinic Network criteria and Simon Broome criteria may also be used which incorporate cholesterol levels, family history, clinical findings, and physical manifestations. Aggressive lipid-lowering therapy is recommended to achieve LDL-C reductions of at least 50%.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Nexletol. All approvals are provided for the duration noted below. A patient who has previously met Initial Therapy criteria for Nexletol for the requested indication under the Coverage Review Department and is currently receiving Nexletol is only required to meet continuation of therapy criteria (i.e., currently receiving therapy). If past criteria has not been met under the Coverage Review Department and the patient is currently receiving Nexletol, or is restarting Nexletol, Initial Therapy criteria must be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nexletol is recommended in those who meet the following criteria:

FDA-Approved Indications

96. Atherosclerotic Cardiovascular Disease.* Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets all of the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient has had one of the following conditions or diagnoses (a, b, c, d, or e):

a) A previous myocardial infarction or a history of an acute coronary syndrome; OR
b) Angina (stable or unstable); OR
c) A past of stroke or transient ischemic attack; OR
d) Peripheral arterial disease; OR
e) Patient has undergone a coronary or other arterial revascularization procedure in the past; AND
Note: Examples include coronary artery bypass graft surgery, percutaneous coronary intervention, angioplasty, and coronary stent procedures.

iii. Patient meets one of the following (a or b):
a) Patient meets all of the following [(1), (2), and (3)]:
(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single entity or as a combination product]); AND
(2) Patient has tried one high-intensity statin above along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND
(3) Low-density lipoprotein cholesterol level after this treatment regimen remains ≥ 70 mg/dL; OR
b) Patient has been determined to be statin intolerant by meeting one of the following [(1) or (2)]:
(1) Patient experienced statin-related rhabdomyolysis; OR
Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR
(2) Patient meets all of the following [(a), (b), and (c)]:
(a) Patient experienced skeletal-related muscle symptoms; AND
Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).
(b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND
(c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); OR
Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

B) Patient Currently Receiving Nexletol. Approve if according to the prescriber, the patient has experienced a response to therapy.
Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Nexletol for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Nexletol, Initial Therapy criteria must be met.

44. Heterozygous Familial Hypercholesterolemia (HeFH).* Approve for 1 year if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve if the patient meets all of the following (i, ii, and iii):
i. Patient is ≥ 18 years of age; AND
ii. Patient meets one of the following (a, b, or c):

a) Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents); OR

b) Patient has genetic confirmation of HeFH by mutations in the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9, or low-density lipoprotein receptor adaptor protein 1 gene; OR

c) Patient has been diagnosed with heterozygous familial hypercholesterolemia meeting one of the following diagnostic criteria thresholds [(1) or (2)]:

(1) Prescriber confirms that the Dutch Lipid Network criteria score was > 5; OR

(2) Prescriber confirms that Simone Broome criteria met the threshold for "definite" or "possible (or probable)" familial hypercholesterolemia; AND

iii. Patient meets one of the following (a or b):

a) Patient meets all of the following [(1), (2), and (3)]:

(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]); AND

(2) Patient has tried one high-intensity statin above along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND

(3) LDL-C level after this treatment regimen remains ≥ 70 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting one of the following [(1) or (2)]:

(1) Patient experienced statin-related rhabdomyolysis; OR

Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR

(2) Patient meets all of the following [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND

Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

(b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND

(c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); OR

Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

B) Patient Currently Receiving Nexletol. Approve if according to the prescriber, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Nexletol for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Nexletol, Initial Therapy criteria must be met.

Other Uses with Supportive Evidence

45. Primary Hyperlipidemia.* Approve for 1 year if the patient meets ONE of the following (A or B):
Note: This is not associated with atherosclerotic cardiovascular disease (ASCVD) or heterozygous familial hypercholesterolemia (HeFH) and may be referred to as combined hyperlipidemia, hypercholesterolemia (pure, primary), dyslipidemia, or increased/elevated low-density lipoprotein cholesterol (LDL-C) levels.

A) Initial Therapy. Approve if the patient meets all of the following (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has a coronary artery calcium or calcification score ≥ 300 Agatston units; AND
- **iii.** Patient meets one of the following (a or b):
  - **a)** Patient meets all of the following [(1), (2), and (3)]:
    - **(1)** Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]); AND
    - **(2)** Patient has tried the one high-intensity statin therapy above along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND
    - **(3)** LDL-C level after this treatment regimen remains ≥ 100 mg/dL; OR
  - **b)** Patient has been determined to be statin intolerant by meeting one of the following [(1) or (2)]:
    - **(1)** Patient experienced statin-related rhabdomyolysis; OR
      Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]).
    - **(2)** Patient meets all of the following [(a), (b), and (c)]:
      - **(a)** Patient experienced skeletal-related muscle symptoms; AND
        Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).
      - **(b)** The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND
      - **(c)** When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); OR
        Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

B) Patient Currently Receiving Nexletol. According to the prescriber, the patient has experienced a response to therapy.
Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Nexletol for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Nexletol, Initial Therapy criteria must be met.

Note:
* A patient may have diagnoses that pertain to more than one indication, therefore, consider review under different approval conditions, if applicable (e.g., a patient with heterozygous familial

hypercholesterolemia may have had a clinical ASCVD event, a patient with primary hyperlipidemia may have heterozygous familial hypercholesterolemia).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nexletol is not recommended in the following situations:

152. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX A

Simon Broome Register Diagnostic Criteria.[15]
LDL-C – Low-density lipoprotein cholesterol; LDL – Low-density lipoprotein; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

APPENDIX B.

Dutch Lipid Network Criteria.[9]

LDL-C – Low-density lipoprotein cholesterol; CAD – Coronary artery disease; LDLR – Low-density lipoprotein receptor; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

PRIOR AUTHORIZATION POLICY

POLICY: Hyperlipidemia – Nexlizet Prior Authorization Policy
- Nexlizet® (bempedoic acid and ezetimibe tablets – Esperion)

REVIEW DATE: 04/26/2023

OVERVIEW

Nexlizet contains bempedoic acid, an adenosine triphosphate-citrate lyase inhibitor, and ezetimibe, a cholesterol absorption inhibitor. It is indicated as an adjunct to diet and statin therapy for the treatment primary hyperlipidemia in adults with the following:[1]

- **Atherosclerotic cardiovascular disease (ASCVD)** for those who require additional lowering of low-density lipoprotein cholesterol (LDL-C).
- **Heterozygous familial hypercholesterolemia** (HeFH) for those who require additional lowering of LDL-C.

The safety and effectiveness have not been established in pediatric patients.[1]

Guidelines

Many guidelines are available regarding the treatment of patients with dyslipidemia which include the management of HeFH and ASCVD.[2-7] For patients with elevated LDL-C, statins are the cornerstone of therapy and recommended first-line to be used at maximally tolerated doses due to the established benefits regarding the reduction of CV risks. Atorvastatin 40 mg to 80 mg once daily (QD) and rosuvastatin 20 mg to 40 mg QD are considered high-intensity statins as they achieve LDL-C lowering of ≥ 50%.

- The **American College of Cardiology Expert Consensus Decision Pathway on the Role of Non-Statin Therapies** for LDL-Cholesterol Lowering in the Management of ASCVD Risk (2022) make several recommendations; Nexletol® (bempedoic acid tablets) is addressed.[2] For adults with clinical ASCVD at very high risk (e.g., patients with major ASCVD events, HeFH, diabetes) who are on statin therapy for secondary prevention, the general goal is ≥ 50% LDL-C reduction and an LDL-C < 55 mg/dL (of non-HDL-C < 85 mg/dL) with maximally tolerated statin therapy. If the above goals are not achieved, the initial non-statin agents recommended include ezetimibe and/or a proprotein convertase subtilisin kexin type 9 monoclonal antibody (i.e., Repatha or Praluent). Nexletol can be considered after these therapies.
    - The **American Association of Clinical Endocrinologists and American College of Endocrinology** has guidelines regarding the management of dyslipidemia and the prevention of CV disease (2020).[7] Nexletol is mentioned is cited as an option for intensification of therapy after use of standard agents such as high-intensity/moderate-intensity statins.
    - The **American Heart Association (AHA)/American College of Cardiology** guidelines on the management of blood cholesterol (2018) define ACSVD as acute coronary syndrome (ACS), those with a history of myocardial infarction, stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack, or peripheral arterial disease.[3,4] An LDL-C < 70 mg/dL is recommended for most patients with ASCVD to reduce CV risk.
    - **The AHA** published a scientific statement regarding familial hypercholesterolemia (2015).[8] Key points are that the condition may start early (in childhood or adolescence) and is noted by LDL-C levels ≥ 190 mg/dL. Premature CV disease can result. Diagnosis can be confirmed by genetic testing. The Dutch Lipid Clinic Network criteria and Simon

Broome criteria may also be used which incorporate cholesterol levels, family history, clinical findings, and physical manifestations. Aggressive lipid-lowering therapy is recommended to achieve LDL-C reductions of at least 50%.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Nexlizet. All approvals are provided for the duration noted below. A patient who has previously met Initial Therapy criteria for Nexlizet for the requested indication under the Coverage Review Department and is currently receiving Nexlizet is only required to meet continuation of therapy criteria (i.e., currently receiving therapy). If past criteria has not been met under the Coverage Review Department and the patient is currently receiving Nexlizet, or is restarting Nexlizet, Initial Therapy criteria must be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nexlizet is recommended in those who meet the following criteria:

FDA-Approved Indications

97. Atherosclerotic Cardiovascular Disease. Approve for 1 year if the patient meets all of the following (A or B):

A) Initial Therapy. Approve if the patient meets all of the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient has had one of the following conditions or diagnoses (a, b, c, d or e):

a) A previous myocardial infarction or a history of an acute coronary syndrome; OR

b) Angina (stable or unstable); OR

c) A past of stroke or transient ischemic attack; OR

d) Peripheral arterial disease; OR

e) Patient has undergone a coronary or other arterial revascularization procedure in the past; AND

Note: Examples include coronary artery bypass graft surgery, percutaneous coronary intervention, angioplasty, and coronary stent procedures.

iii. Patient meets one of the following criteria (a or b):

a) Patient meets both of the following [(1) and (2)]:

(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND

(2) Low-density lipoprotein cholesterol level after therapy regimen remains ≥ 70 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting one of the following criteria [(1) or (2)]:

(1) Patient experienced statin-related rhabdomyolysis; OR

Note: Statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR

(2) Patient meets all of the following [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND
Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).
(b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND
(c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); OR
Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

B) Patient Currently Receiving Nexlizet. Approve if according to the prescriber, the patient has experienced a response to therapy.
Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Nexlizet for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Nexlizet, Initial Therapy criteria must be met.

46. Heterozygous Familial Hypercholesterolemia (HeFH). Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets all of the following (i, ii, or iii):
i. Patient is ≥ 18 years of age; AND
ii. Patient meets one of the following criteria (a, b, or c):
a) Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents); OR
b) Patient has genetic confirmation of heterozygous familial hypercholesterolemia by mutations in the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9 or low-density lipoprotein receptor adaptor protein 1 gene; OR
c) Patient has been diagnosed with heterozygous familial hypercholesterolemia by meeting one of the following diagnostic criteria thresholds [(1) or (2)]:
(1) Prescriber confirms that the Dutch Lipid Network criteria score was > 5; OR
(2) Prescriber confirms that Simone Broome criteria met the threshold for "definite" or "possible (or probable)" familial hypercholesterolemia; AND
iii. Patient meets one of the following (a or b):
a) Patient meets both of the following [(1) and (2)]:
(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND
(2) LDL-C level after this treatment regimen remains ≥ 70 mg/dL; OR
b) Patient has been determined to be statin intolerant by meeting one of the following [(1) or (2)]:
(1) Patient experienced statin-related rhabdomyolysis; OR
Note: Statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR
(2) Patient meets all of the following [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND
Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).
(b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND
(c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); OR
Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

B) Patient Currently Receiving Nexlizet. Approve if according to the prescriber, the patient has experienced a response to therapy.
Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Nexlizet for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Nexlizet, Initial Therapy criteria must be met.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nexlizet is not recommended in the following situations:

153. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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APPENDIX A

Simon Broome Register Diagnostic Criteria.[9]
LDL-C – Low-density lipoprotein cholesterol; LDL – Low-density lipoprotein; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

APPENDIX B.

Dutch Lipid Network Criteria.[8]

LDL-C – Low-density lipoprotein cholesterol; CAD – Coronary artery disease; LDLR – Low-density lipoprotein receptor; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

PRIOR AUTHORIZATION POLICY

POLICY: Hyperlipidemia – Omega-3 Fatty Acid Products
- Lovaza® (omega-3-acid ethyl esters capsules – GlaxoSmithKline, generic)
- Vascepa® (icosapent ethyl capsules – Amarin, generic)

REVIEW DATE: 01/25/2023

OVERVIEW

Lovaza, a combination of ethyl esters of omega-3 fatty acids (mainly eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) and Vascepa, an ethyl ester of EPA, are indicated for **hypertriglyceridemia** (severe, triglyceride [TG] levels ≥ 500 mg/dL), to reduce TG levels as an adjunct to diet in adults.[1,2]

Vascepa is also indicated to **reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina** requiring hospitalization in adults with elevated TG levels (≥ 150 mg/dL) and either established cardiovascular (CV) disease or diabetes mellitus with two or more additional risk factors for CV disease, as an adjunct to maximally tolerated statin therapy.[2,3]

Lovaza and Vascepa have been studied in patients with TG levels ≥ 200 mg/dL and < 500 mg/dL in patients who had persistently high TGs despite treatment with statin therapy and proper dietary modifications.[4,5] In these short-term trials lasting 6 to 12 weeks in duration, the addition of omega-3 fatty acid therapy led to further reductions in TG levels.

Guidelines/Scientific Statements

Several guidelines are available that discuss the management of elevated TG values and have incorporated omega-3 fatty acid products.[6-11] Highlights from a few guidelines are below.

- The American College of Cardiology Expert Consensus Decision Pathway on the Management of Atherosclerotic Cardiovascular Disease (ASCVD) Risk Reduction in Patients with Persistent Hypertriglyceridemia (2021) recommends Vascepa in a variety of clinical scenarios in patients with persistent fasting hypertriglyceridemia (150 to 499 mg/dL).[6] Also, Lovaza and Vascepa are recommended in several circumstances in which patients have very elevated TG levels (≥ 500 mg/dL).
- The American Diabetes Association Standards of Care (2023) state that Vascepa should be considered for patients with ASCVD or other CV risk factors on a statin with controlled low-density lipoprotein cholesterol levels but with elevated TG levels (135 to 499 mg/dL) to reduce CV risk.[10]
- The National Lipid Association (NLA) published a scientific statement regarding Vascepa (2019).[11] Based on the REDUCE-IT trial, the NLA position is that for patients ≥ 45 years of age with clinical ASCVD, or ≥ 50 years of age with diabetes mellitus requiring medication plus at least one additional risk factor, with fasting TG levels of 135 to 499 mg/dL on high-intensity or maximally tolerated statin therapy (with or without ezetimibe), treatment with Vascepa is recommended for ASCVD risk reduction (Class I evidence rating).

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of omega-3 fatty acid products (Lovaza and Vascepa [both brand and generic]). All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of **Vascepa** (brand and generic) is recommended in those who meet the following criteria:

FDA-Approved Indication

37. Cardiovascular Risk Reduction in a Patient with Elevated Triglycerides. Approve Vascepa (brand or generic) for 1 year if the patient meets all of the following criteria (A, B, and C):
- **A)** Patient meets one of the following (i or ii):
  - **i.** Patient has established cardiovascular disease; OR
    Note: Examples of cardiovascular disease include a previous myocardial infarction; a history of an acute coronary syndrome event; angina (stable or unstable); past history of stroke or transient ischemic attack; peripheral arterial disease; or the patient has undergone a coronary or other arterial revascularization procedure in the past (e.g., coronary artery bypass graft, percutaneous coronary intervention, angioplasty, coronary stent procedure); OR
  - **ii.** Patient meets both of the following (a and b):
    - **a)** Patient has diabetes; AND
    - **b)** According to the prescriber, has at least two additional risk factors for cardiovascular disease.
      Note: Examples of risk factors for cardiovascular disease include hypertension; low high-density lipoprotein cholesterol levels (e.g., ≤ 40 mg/dL); renal dysfunction (creatinine clearance < 60 mL/min); family of premature coronary disease; presence of albuminuria; current cigarette smoking; familial hypercholesterolemia; and increased weight (body mass index greater than 25 kg/m^2); AND
- **B)** Prior to initiation of therapy, the patient has a fasting baseline triglyceride level ≥ 150 mg/dL; AND
- **C)** Patient meets one of the following criteria (i or ii):
  - **i.** Patient is receiving statin therapy; OR
  - **ii.** According to the prescriber the patient cannot tolerate statin therapy.

II. Coverage of **Lovaza** and **Vascepa** (both brand and generic) is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. Hypertriglyceridemia with Triglyceride Levels ≥ 500 mg/dL. Approve Lovaza or Vascepa (both brand or generic) for 1 year if the patient meets the following criteria (A and B):
- **A)** Prior to initiation of therapy, the patient has a fasting baseline triglyceride level ≥ 500 mg/dL; AND
- **B)** Patient has tried, or is currently receiving, one of the following products: niacin (immediate-release or extended-release), a fibrate, or a statin.
  Note: Examples of fibrates include gemfibrozil, fenofibrate, and fenofibric acid. Examples of statins include atorvastatin, rosuvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, and Livalo (pitavastatin tablets). Also, a patient who requests Vascepa may potentially be reviewed under the criteria for Cardiovascular Risk Reduction in a Patient with Elevated Triglycerides.

Other Uses with Supportive Evidence

2. **Hypertriglyceridemia with Triglyceride Levels of 150 mg/dL to < 500 mg/dL.** Approve Lovaza or Vascepa (both brand or generic) for 1 year if the patient meets the following criteria (A and B):
   A) Prior to initiation of therapy, the patient has a fasting baseline triglyceride level of 150 mg/dL to < 500 mg/dL; AND
   B) Patient has tried, or is currently receiving, one of the following products: niacin (immediate-release or extended-release), a fibrate, or a statin.
   Note: Examples of fibrates include gemfibrozil, fenofibrate, and fenofibric acid. Examples of statins include atorvastatin, rosuvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, and Livalo (pitavastatin tablets). Also, a patient who requests Vascepa may potentially be reviewed under the criteria for Cardiovascular Risk Reduction in Patients with Elevated Triglycerides.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lovaza and Vascepa (both brand and generic) is not recommended in the following situations:

45. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Hypoactive Sexual Desire Disorder – Addyi Prior Authorization Policy
- Addyi™ (flibanserin tablets – Sprout)

REVIEW DATE: 01/03/2024

OVERVIEW

Addyi is indicated for the **treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD)** that is characterized by low sexual desire that causes marked distress or interpersonal difficulty and is NOT due to a co-existing medical or psychiatric condition; problems within the relationship; or the effects of a medication or other drug substance.[1] Addyi is not indicated for the treatment of HSDD in postmenopausal women or in men. It is also not indicated to enhance sexual performance. The prescribing information notes that Addyi should be discontinued after 8 weeks if the patient does not report any improvement in HSDD symptoms.[1] In the Addyi clinical studies, one of the coprimary efficacy endpoints was assessed by the median increase in the number of satisfying sexual events standardized over a 28-day period.

Safety

Addyi contains a Boxed Warning regarding the use of alcohol and the increase in risk of severe hypotension and syncope.[1] Patients should be counseled to wait at least two hours after consuming one or two standard alcoholic drinks before taking Addyi or skip the dose if they have consumed three or more standard alcoholic drinks that evening.

Guidelines

The American College of Obstetricians and Gynecologists guideline on Female Sexual Dysfunction (2019) notes the importance of recognizing if the loss of sexual interest is due to a co-morbid or undiagnosed condition, or medication.[4] The guidelines note that Addyi was approved in 2015 by the FDA to treatment hypoactive sexual desire disorder in premenopausal women without depression. Addyi is noted as a treatment option for HSDD in premenopausal women without depression who are appropriately counseled about the risk of alcohol use during treatment.[4] The guidelines also discuss that systemic review and meta-analysis of existing studies with Addyi show that although the studies were randomized, their overall quality of evidence for efficacy and safety was very low.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Addyi. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Addyi is recommended in those who meet the following criteria:

FDA-Approved Indication

47. Hypoactive Sexual Desire Disorder (HSDD)/Female Sexual Interest/Arousal Disorder (FSIAD). Approve for the duration noted if the patient meets ONE of the following (A or B):

5. Initial Therapy. Approve for 8 weeks if the patient meets the following (i, ii, iii, iv, v, and vi):

- **i.** Patient is premenopausal; AND
- **ii.** Patient's symptoms of HSDD/FSIAD have persisted for a minimum of 6 months; AND
- **iii.** Patient has had normal sexual desire in the past, prior to the diagnosis of HSDD/FSIAD; AND
- **iv.** Patient does **not** have a diagnosis of depression; AND
- **v.** Other known causes of HSDD/FSIAD, such as co-existing medical or psychiatric conditions, problems within a relationship, effects of medications (e.g., antidepressants), or drug abuse have been ruled out by the prescriber; AND
- **vi.** The prescriber has counseled the patient regarding the interaction with alcohol and Addyi, and the increased risk of hypotension and syncope.

6. Patient is Currently Receiving Addyi. Approve for 6 months if the patient meets the following (i, ii, and iii):

- **i.** Patient is premenopausal; AND
- **ii.** The prescriber confirms that since initiating Addyi therapy, the patient reports a significant improvement in sexual desire and/or a decrease in sexual distress; AND
- **iii.** Patient has not reported any serious or concerning adverse events (e.g., hypotension, syncope, dizziness) while taking Addyi.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Addyi is not recommended in the following situations:

46. Postmenopausal Patients. Two published Phase III trials assessed the efficacy of Addyi in postmenopausal women with HSDD.[2,3] In the SNOWDROP trial though there was statistical significance in the primary endpoints (number of satisfying sexual events over 28 days and increase in desire score), the treatment difference between Addyi and placebo was very minimal.[2] The PLUMERIA study was discontinued early by the study sponsor for commercial reasons; however, published data are available for up to Week 16.[3] The improvement from baseline to Week 16 in the Female Sexual Function Index desire domain was significantly greater with Addyi compared with placebo, but the other co-primary endpoint of sexually satisfying events was not significantly different between Addyi and placebo. Addyi is currently not approved for use in postmenopausal women with HSDD/FSIAD symptoms.

47. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Hypoactive Sexual Desire Disorder – Vyleesi Prior Authorization Policy
- Vyleesi™ (bremelanotide subcutaneous injection – Palatin)

REVIEW DATE: 01/03/2024

OVERVIEW

Vyleesi is indicated for the **treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD)** as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is NOT due to: a co-existing medical or psychiatric condition, problems with the relationship, or effects of a medication or drug substance. Limitations of Use: Vyleesi is not indicated for the treatment of HSDD in postmenopausal women or in men. Vyleesi is not indicated to enhance sexual performance.[1] In Vyleesi pivotal studies, patients were excluded if they were diagnosed with or being treated for depression, psychosis, bipolar disorder, or substance abuse within 6 months before screening.[2] The prescribing information for Vyleesi notes that it should be discontinued after 8 weeks if the patient does not report an improvement in symptoms.[1]

Guidelines

The American College of Obstetricians and Gynecologists guideline on Female Sexual Dysfunction (2019) notes the importance of recognizing if the loss of sexual interest is due to a co-morbid or undiagnosed condition, or medication.[3] Consultation with or referral to a mental health specialist with expertise and training in the treatment of female sexual dysfunction (e.g., sex therapists, psychologists, marriage/relationship counselors) should be considered based on the physician's level of expertise and the patient's individual needs. The guideline does not address Vyleesi.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vyleesi. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vyleesi is recommended in those who meet the following criteria:

FDA-Approved Indications

98. Hypoactive Sexual Desire Disorder (HSDD)/Female Sexual Interest/Arousal Disorder (FSIAD).
Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 8 weeks if the patient meets the following (i, ii, iii, iv, and v):
- **i.** Patient is premenopausal; AND
- **ii.** Patient's symptoms of HSDD/FSIAD have persisted for a minimum of 6 months; AND
- **iii.** Patient has had normal sexual desire in the past, prior to the diagnosis of HSDD/FSIAD; AND
- **iv.** Patient has not been diagnosed or treated with depression within the previous 6 months; AND

v. Other known causes of HSDD/FSIAD, such as co-existing medical or psychiatric conditions, problems within a relationship, effects of medications (e.g., antidepressants), or drug abuse have been ruled out by the prescriber.

B) Patient is Currently Receiving Vyleesi. Approve for 6 months if patient meets the following (i and ii):

i. Patient is premenopausal; AND

ii. The prescriber confirms that since initiating Vyleesi therapy, the patient reports a significant improvement in sexual desire and/or a decrease in sexual distress.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vyleesi is not recommended in the following situations:

154. Postmenopausal Patients. Pivotal trials for Vyleesi included only premenopausal women with acquired, generalized hypoactive sexual desire disorder.[1]

155. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Idiopathic Pulmonary Fibrosis and Related Lung Disease – Ofev Prior Authorization Policy

- Ofev® (nintedanib capsules – Boehringer Ingelheim)

REVIEW DATE: 06/28/2023

OVERVIEW

Ofev, a kinase inhibitor, is indicated for the following uses:[1]

- **Idiopathic pulmonary fibrosis** (IPF), treatment.
- **Interstitial lung diseases, chronic fibrosing with a progressive phenotype**, treatment.
- **Interstitial lung disease associated with systemic sclerosis**, to slow the rate of decline in pulmonary function.

The safety and effectiveness of Ofev in pediatric patients have not been established.[1]

Disease Overview

IPF is a form of chronic interstitial lung pneumonia associated with histologic pattern of usual interstitial pneumonia (UIP).[2] The condition is specific for patients that have clinical features and the histologic pattern of UIP or a classical high-resolution computed tomography (HRCT) scan for IPF. In this lung condition there is cellular proliferation, interstitial inflammation, fibrosis, or the combination of these findings, within the alveolar wall that is not due to infection or cancer.[3] IPF is rather rare and the prevalence in the US ranges from 10 to 60 cases per 100,000. However, in one study, the prevalence was 494 cases per 100,000 in 2011 in adults > 65 years of age, which is higher than previous information. The disease mainly impacts older adults.[2] Symptoms include a progressive dry cough and exertional dyspnea. Patients experience a high disease burden with hospital admissions. The clinical course varies among patients but the mean survival after symptom onset is usually 3 to 5 years. The cause is unknown but environmental and occupational hazards may play a role, as well as a of smoking. Medical therapy is only modestly effective and mainly shows the rate of disease progression. Agents FDA-approved for IPF are Ofev and Esbriet® (pirfenidone capsules and film-coated tablets). Lung transplantation is a therapeutic option.

Interstitial lung disease is a common manifestation of systemic sclerosis and is a leading cause of death.[4-6] Among patients who have systemic sclerosis, up to one-half of patients may have interstitial lung disease.[7] The estimate prevalence and annual incidence of systemic sclerosis-associated interstitial lung disease is 1.7 to 4.2 and 0.1 to 0.4 per 100,000 individuals, respectively.[7] However, it is notable that systemic sclerosis is a connective disease that it not limited to the lungs but impacts the skin, blood vessels, heart, kidneys, gastrointestinal tract, and musculoskeletal system. The condition displays great heterogeneity and can be challenging to treat.[4] When the disease affects the internal organs, significant morbidity and mortality may result. Mycophenolate, cyclophosphamide, and azathioprine are immunosuppressants that are utilized in the treatment of interstitial lung disease associated with systemic sclerosis. Corticosteroids are also used. Besides Ofev, Actemra® (tocilizumab subcutaneous injection) is also indicated for use in patients with systemic sclerosis-associated interstitial lung disease.

Clinical Efficacy

Idiopathic Pulmonary Fibrosis (IPF)

The clinical efficacy of Ofev if patients with IPF was established in one Phase II study and two Phase III studies that were identical in design (n = 1,231).[1,8,9] The trials were randomized, double-blind, placebo-controlled studies comparing treatment with Ofev 150 mg twice daily with placebo for 52 weeks. In the two Phase III studies, patients were ≥ 40 years of age and had a forced vital capacity (FVC) ≥ 50% of the predicted value. The diagnosis was confirmed by HRCT and, if available, surgical lung biopsy specimens were assessed. For all three studies, a statistically significant reduction in the annual rate of decline of FVC was observed in patients receiving Ofev compared with patients receiving placebo. Also, data shows that the proportion of patients that demonstrated categorical declines in lung function was lower for patients given Ofev compared with placebo. Acute IPF exacerbations were also reduced.[1,8,9] Some information suggests that patients who have FVC < 50% of predicted may also have some benefits from therapy.[10-13]

Interstitial Lung Diseases, Chronic Fibrosing with a Progressive Phenotype

The efficacy of Ofev was assessed in patients ≥ 18 years of age with chronic fibrosis interstitial lung diseases with a progressive phenotype in a Phase III, double-blind, placebo-controlled trial (INBUILD) [n = 663].[1,14,15] Patients received Ofev 150 mg BID or placebo for at least 52 weeks and the main endpoint was the annual rate in decline in FVC over 52 weeks. Patients who had a clinical diagnosis of chronic fibrosing interstitial lung disease were involved in the trial if they had relevant fibrosis (greater than 10% fibrotic features) and had clinical signs of progression (e.g., FVC decline ≥ 10%, recent FVC decline ≥ 5% but < 10% with worsening symptoms or imaging, or worsening symptoms and worsening imaging). Patients were required to have an FVC ≥ 45% of predicted and a diffusing capacity of the lung for carbon monoxide of at least 30% and < 80% of predicted.

Interstitial Lung Disease Associated with Systemic Sclerosis

The efficacy of Ofev was established in SENSCIS, a randomized, double-blind, placebo-controlled Phase III trial in patients ≥ 18 years of age with systemic sclerosis-related interstitial lung disease (n = 576).[15] Patients were randomized to Ofev or placebo for at least 52 weeks and up to 100 weeks. Patients had ≥ 10% fibrosis on a chest HRCT scan conducted within the previous 12 months and had an FVC ≥ 40% of predicted. The primary efficacy endpoint was the annual rate of decline in FVC over 52 weeks. The annual rate of decline of FVC over 52 weeks was significantly reduced by 41 mL in patients receiving Ofev vs. placebo (-52 mL for Ofev vs. -93 mL with placebo).

Guidelines

In 2015, the clinical practice guideline from the American Thoracic Society (ATS), European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT) on the treatment of IPF were updated.[16] Regarding Ofev, the guideline suggests use of this medication (conditional recommendation, moderate confidence in estimates of effect). The guideline notes that the data with Ofev focuses on patients with IPF who have mild to moderate impairment in pulmonary function tests. It is not known if the benefits would differ among patients with more severe impairment in pulmonary function testing or in patients who have other comorbidities.[16] Updated recommendations by this group in 2022 support use of Ofev in patients with IPF.[17] Regarding the treatment of progressive pulmonary fibrosis, Ofev is a suggested treatment in patients who have failed standard management for fibrotic interstitial lung disease (e.g., immunosuppressive treatment) other than IPF.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ofev. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of

patients treated with Ofev, approval requires Ofev to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Ofev is recommended in those who meet the following criteria:

FDA-Approved Indications

48. Idiopathic Pulmonary Fibrosis. Approve for 1 year if the patient meets one of the following (A or B):
- **7.** Initial Therapy. Approve if the patient meets the following (i, ii, iii, and iv):
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** Forced vital capacity is ≥ 40% of the predicted value; AND
  - **iii.** The diagnosis is confirmed by one of the following (a or b):
    - **a)** Findings on high-resolution computed tomography indicate usual interstitial pneumonia; OR
    - **b)** A surgical lung biopsy demonstrates usual interstitial pneumonia; AND
  - **iv.** Medication is prescribed by or in consultation with a pulmonologist; OR
- **8.** Patient is Currently Receiving Ofev. Approve if the patient meets the following (i, ii and iii):
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** Patient has experienced a beneficial response to therapy over the last year while receiving Ofev; AND

    Note: For a patient who has received less than 1 year of therapy, response is from baseline prior to initiating Ofev. Examples of a beneficial response include a reduction in the anticipated decline in forced vital capacity, six-minute walk distance, and/or in the number or severity of idiopathic pulmonary fibrosis exacerbations.
  - **iii.** Medication is prescribed by or in consultation with a pulmonologist.

49. Interstitial Lung Diseases, Chronic Fibrosing with a Progressive Phenotype. Approve for 1 year if the patient meets one of the following (A or B):
Note: Examples of conditions include hypersensitivity pneumonitis; idiopathic non-specific interstitial pneumonitis; idiopathic non-specific interstitial pneumonia; unclassifiable idiopathic interstitial pneumonia; autoimmune interstitial lung disease (e.g., rheumatoid arthritis interstitial lung disease); exposure-related interstitial lung disease; and mixed connective tissue disease interstitial lung disease. This is not associated with idiopathic pulmonary fibrosis (see indication above).
- **A)** Initial Therapy. Approve if the patient meets the following (i, ii, iii, iv, and v):
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** Forced vital capacity is ≥ 40% of the predicted value; AND
  - **iii.** According to the prescriber, the patient has fibrosing lung disease impacting more than 10% of lung volume on high-resolution computed tomography; AND
  - **iv.** According to the prescriber, the patient has clinical signs of progression; AND

    Note: Examples of clinical signs of progression include a forced vital capacity decline ≥ 10% of the predicted value or forced vital capacity decline ≥ 5% to < 10% with worsening symptoms and/or worsening imaging.
  - **v.** Medication is prescribed by or in consultation with a pulmonologist; OR
- **B)** Patient is Currently Receiving Ofev. Approve if the patient meets the following (i, ii, and iii):
  - **i.** Patient is ≥ 18 years of age; AND

ii. Patient has experienced a beneficial response to therapy over the last year while receiving Ofev; AND

Note: For a patient who has received less than 1 year of therapy, response is from baseline prior to initiating Ofev. Examples of a beneficial response include a reduction in the anticipated decline in forced vital capacity, six-minute walk distance, and/or in the number or severity of interstitial lung disease-related exacerbations.

iii. Medication is prescribed by or in consultation with a pulmonologist.

50. Interstitial Lung Disease Associated with Systemic Sclerosis. Approve for 1 year if the patient meets one of the following (A or B):

A) Initial Therapy. Approve if the patient meets the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Forced vital capacity is ≥ 40% of the predicted value; AND

iii. Diagnosis is confirmed by high-resolution computed tomography; AND

iv. Medication is prescribed by or in consultation with a pulmonologist or a rheumatologist; OR

B) Patient is Currently Receiving Ofev. Approve if the patient meets the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient has experienced a beneficial response to therapy over the last year while receiving Ofev; AND

Note: For a patient who has received less than 1 year of therapy, response is from baseline prior to initiating Ofev. Examples of a beneficial response include a reduction in the anticipated decline in forced vital capacity, six-minute walk distance, and/or in the number or severity of disease-related exacerbations.

iii. Medication is prescribed by or in consultation with a pulmonologist or a rheumatologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ofev is not recommended in the following situations:

48. Ofev is Being Used Concomitantly with Esbriet (pirfenidone capsules). Esbriet is another medication indicated for IPF. The effectiveness and safety of concomitant use of Ofev with Esbriet have not been established. The 2015 ATS/ERS/JRS/ALAT clinical practice guideline regarding the treatment of idiopathic pulmonary fibrosis (an update of the 2011 clinical practice guideline) does not recommend taking Ofev and Esbriet in combination.[16] A small exploratory study was done in which patients with IPF receiving Ofev added on to Esbriet.[18] Further research is needed to determine the utility of this combination regimen.

49. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Idiopathic Pulmonary Fibrosis and Related Lung Disease – Pirfenidone Prior Authorization Policy

- Esbriet® (pirfenidone capsules and film-coated tablets – Genentech, generic)

REVIEW DATE: 06/28/2023

OVERVIEW

Pirfenidone, a pyridone, is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).[1] The safety and effectiveness of pirfenidone in pediatric patients have not been established.

Disease Overview

IPF is a form of chronic interstitial lung pneumonia associated with histologic pattern of usual interstitial pneumonia (UIP).[2] The condition is specific for patients that have clinical features and the histologic pattern of UIP or a classical high-resolution computed tomography scan for IPF. In this lung condition there is cellular proliferation, interstitial inflammation, fibrosis, or the combination of these findings, within the alveolar wall that is not due to infection or cancer.[3] IPF is rather rare and the prevalence in the US ranges from 10 to 60 cases per 100,000. However, in one study, the prevalence was 494 cases per 100,000 in 2011 in adults > 65 years of age, which is higher than previous information. The disease mainly impacts older adults.[2] Symptoms include a progressive dry cough and exertional dyspnea. Patients experience a high disease burden with hospital admissions. The clinical course varies among patients but the mean survival after symptom onset is usually 3 to 5 years. The cause is unknown but environmental and occupational hazards may play a role, as well as a of smoking. Medical therapy is only modestly effective and mainly shows the rate of disease progression. Agents FDA-approved for IPF are Ofev® (nintedanib capsules) and pirfenidone. Lung transplantation is a therapeutic option.

Clinical Efficacy

The efficacy of pirfenidone was assessed in patients with IPF in three Phase III, randomized, double-blind, placebo-controlled, multicenter, multinational trials (n = 1,247).[1,4,5] Patients were required to have a percent predicted forced vital capacity (%FVC) ≥ 50% at baseline. Pirfenidone 2,403 mg/day led to a statistically significant change in the %FVC at 52 weeks and 72 weeks, respectively. Also, a reduction in the mean decline in forced vital capacity (in mL) was observed in both studies for patients receiving pirfenidone 2,403 mg/day compared with placebo.[1-3] Some information suggests that patients who have %FVC < 50% may also have some benefits from therapy.[6-9]

Guidelines

In 2015, the clinical practice guideline from the American Thoracic Society (ATS), European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT) on the treatment of IPF was updated.[10] Regarding pirfenidone, the guideline suggests use of this medication (conditional recommendation, moderate confidence in estimates of effect). The guideline notes that the data with pirfenidone cannot be generalized to patients with IPF who have more severe impairment of pulmonary function tests or for patients with other significant comorbidities.[10] Updated recommendations by this group in 2022 support use of pirfenidone in patients with IPF.[11]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of pirfenidone. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with pirfenidone, approval requires pirfenidone to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of pirfenidone is recommended in those who meet the following criteria:

FDA-Approved Indication

51. Idiopathic Pulmonary Fibrosis. Approve for 1 year if the patient meets one of the following (A or B):

9. Initial Therapy. Approve if the patient meets the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Forced vital capacity is ≥ 40% of the predicted value; AND

iii. Diagnosis of idiopathic pulmonary fibrosis is confirmed by one of the following (a or b):

(1) Findings on high-resolution computed tomography indicate usual interstitial pneumonia; OR

(2) A surgical lung biopsy demonstrates usual interstitial pneumonia; AND

iv. Medication is prescribed by or in consultation with a pulmonologist; OR

10. Patient is Currently Receiving Pirfenidone. Approve if the patient meets the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient has experienced a beneficial response to therapy over the last year while receiving pirfenidone; AND

Note: For a patient who has received less than 1 year of therapy, response is from baseline prior to initiating pirfenidone. Examples of a beneficial response include a reduction in the anticipated decline in forced vital capacity, six-minute walk distance, and/or a reduction in the number or severity of idiopathic pulmonary fibrosis exacerbations.

iii. Medication is prescribed by or in consultation with a pulmonologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of pirfenidone is not recommended in the following situations:

50. Pirfenidone is Being Used Concomitantly with Ofev (nintedanib capsules). Ofev is another medication indicated for the treatment of IPF. The effectiveness and safety of concomitant use of pirfenidone with Ofev have not been established. The 2015 ATS/ERS/JRS/ALAT clinical practice guideline regarding the treatment of idiopathic pulmonary fibrosis (an update of the 2011 clinical practice guideline) does not recommend taking Ofev and pirfenidone in combination.[10] A small exploratory study was done in which patients with IPF receiving Ofev added on pirfenidone.[12] Further research is needed to determine the utility of this combination regimen.

51. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Immune Disorder – Joenja Prior Authorization Policy
- Joenja® (leniolisib tablets – Pharming)

REVIEW DATE: 03/29/2023; selected revision 04/12/2023

OVERVIEW

Joenja, a kinase inhibitor, is indicated for the treatment of **activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS)** in adults and pediatric patients ≥12 years of age.[1]

Disease Overview

APDS is an ultra-rare, genetic, progressive primary immunodeficiency disorder.[2,3] It is estimated to occur in 1 to 2 people per one million. APDS is an autosomal dominant disease caused by variants in *PIK3CD* or *PIK3R1* genes, resulting in hyperactivation of the PI3Kδ pathway. APDS is characterized by both immune deficiency and dysregulation, which causes various clinical manifestations, such as recurrent sinopulmonary infections, recurrent herpesvirus infections, lymphadenopathy, hepatomegaly, splenomegaly, nodular lymphoid hyperplasia, autoimmunity, cytopenias, enteropathy, and bronchiectasis. APDS can lead to end-organ damage, malignancy, and early mortality. There are no other FDA-approved treatments for APDS. Current APDS management includes immunosuppressants, prophylactic antimicrobials, immunoglobulin replacement therapy, sirolimus, hematopoietic stem cell transplantation (HSCT), and surgery or procedures.

Clinical Efficacy

The efficacy of Joenja was evaluated in one Phase III, randomized, triple-blind, placebo-controlled, multicenter, pivotal study in 31 patients with APDS.[2] Eligible patients were 12 to 75 years of age, had pathogenic variants in *PIK3CD* or *PIK3R1* genes, had clinical findings consistent with APDS (e.g., of repeated oto-sino-pulmonary infection and organ dysfunction), and more than one measurable lymph node on computed tomography or magnetic resonance imaging scan. The co-primary outcomes were differences from baseline in the index lymph node size and the percentage of naïve B cells in peripheral blood, which are measures of immune dysregulation and deficiency.[2] Both co-primary endpoints were met. Joenja significantly reduced lymphadenopathy and significantly increased the percentage of naïve B cells. Joenja also improved other outcome measures, such as spleen size, lymphocyte subsets, cytopenias, and immunoglobulin (Ig)M levels. Although changes in health-related quality of life measures were not statistically significant, many patients reported increase in activity and energy levels. An ongoing open label extension study reported results in an interim analysis from 37 patients with least 5 years of Joenja exposure.[3,4] Joenja demonstrated a reduction in use of immunoglobulin replacement therapy and a decrease in the annualized yearly infection rate. Continued improvements in mean index lymph node size; mean immunoglobulin M (IgM) levels; and mean percentages of naïve B cells and transitional B cells were seen.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Joenja. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Joenja as well as the monitoring required for adverse events and long-term efficacy, approval requires Joenja to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Joenja is recommended in those who meet the following criteria:

FDA-Approved Indication

99. Activated phosphoinositide 3-kinase delta syndrome (APDS). Approve for the duration noted if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets all of the following criteria (i, ii, iii, iv, and v):

- **i.** Patient is ≥ 12 years of age; AND
- **ii.** Patient weighs ≥ 45 kg; AND
- **iii.** Patient has a genetic phosphoinositide 3-kinase delta (PI3Kδ) mutation with a variant in *PIK3CD* and/or *PIK3R1* genes; AND
- **iv.** Patient has at least one clinical finding or manifestation consistent with APDS; AND
  Note: Examples of clinical findings or manifestations of APDS include recurrent sinopulmonary infections, recurrent herpesvirus infections, lymphadenopathy, hepatomegaly, splenomegaly, nodular lymphoid hyperplasia, autoimmunity, cytopenias, enteropathy, bronchiectasis, and organ dysfunction.
- **v.** The medication is prescribed by or in consultation with an immunologist, pulmonologist, gastroenterologist, hematologist, or an infectious diseases physician who treats patients with primary immune deficiencies.

B) Patient is currently receiving Joenja. Approve for 1 year if the patient meets all of the following criteria (i, ii, iii, iv, and v):

- **i.** Patient has been established on therapy for at least 6 months; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy should be considered under criterion A (Initial Therapy).
- **ii.** Patient is ≥ 12 years of age; AND
- **iii.** Patient weighs ≥ 45 kg; AND
- **iv.** Patient has a genetic phosphoinositide 3-kinase delta (PI3Kδ) mutation with a variant in *PIK3CD* and/or *PIK3R1* genes; AND
- **v.** Patient has had a positive clinical response in the signs and manifestations of APDS.
  Note: Examples of positive clinical response in the signs and manifestations of APDS include reduction of: lymph node size, spleen size, immunoglobulin replacement therapy use, infection rate, or immunoglobulin M (IgM) levels.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Joenja is not recommended in the following situations:

156. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Immune Globulin – Atgam Prior Authorization Policy

- Atgam® (lymphocyte immune globulin, anti-thymocyte globulin [equine] intravenous infusion – Pfizer)

REVIEW DATE: 01/03/2024

OVERVIEW

Atgam, an immune globulin, is indicated for the following uses:[1]

- **Allograft rejection**, for the management of allograft rejection in renal transplant patients. When administered with conventional therapy at the time of rejection, Atgam increases the frequency of resolution of the acute rejection episode.
- **Aplastic anemia**, for the treatment of moderate to severe aplastic anemia in patients unsuitable for bone marrow transplantation. The usefulness of Atgam has not been demonstrated in patients with aplastic anemia who are suitable candidates for bone marrow transplantation or in patients with aplastic anemia secondary to neoplastic disease, storage disease, myelofibrosis, Fanconi's syndrome, or in patients known to have been exposed to myelotoxic agents or radiation.

Guidelines

The use of Atgam is supported in a number of clinical guidelines.[2-9]

- **Acute cellular rejection**: The Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Care of Kidney Transplant Recipients (2009), recommend anti-thymocyte globulin (ATG) as a treatment option for induction therapy, given prior to, at the time of, or immediately after transplant.[2] The KDIGO guidelines recommend ATG for the treatment of acute cellular rejection unresponsive to corticosteroids, recurrent acute cellular rejection, and for acute antibody-mediated rejection.
- **Aplastic anemia**: The British Society of Haematology guidelines for the diagnosis and management of aplastic anemia recommends immunosuppressive therapy with Atgam plus cyclosporine for the first-line treatment of patients with non-severe aplastic anemia requiring treatment, severe or very severe aplastic anemia in those who lack a matched sibling donor, and severe or very severe aplastic anemia patients aged > 35 to 50 years of age.[3,4] A second course of Atgam is recommended following a relapse after the first course of therapy, or after failure to respond to the first course if the patient is ineligible for a matched unrelated donor hematopoietic stem cell transplant. In addition, Atgam is included in conditioning regimens for bone marrow transplantation.[5]
- The National Comprehensive Cancer Network (NCCN) guidelines:[6-9]
  - **Graft-vs-host disease:** The NCCN Hematopoietic Cell Transplantation Clinical Practice Guidelines (version 3.2023 – October 9, 2023) recommend ATG as additional therapy in conjunction with corticosteroids for the management of acute steroid-refractory disease.[9]
  - **Immunotherapy-related cardiovascular toxicity:** The NCCN Guidelines for the Management of Immunotherapy-Related Toxicities (version 1.2024 – December 7, 2023), recommend Atgam as additional treatment for life-threatening cardiac immune-related adverse events if there is no improvement within 24 hours of starting pulse-dose methylprednisolone.[6,7] Atgam can also be considered for elevated liver transaminases if there is worsening or no improvement after use with corticosteroids, such as prednisone or methylprednisolone.
  - **Myelodysplastic syndrome:** The NCCN Clinical Practice Guidelines (version 3.2023 – November 10, 2023) recommend Atgam as a treatment option for the management of lower

risk disease.[7,8] Treatment with Atgam alone or in combination with cyclosporine and/or Promacta® (eltrombopag olamine tablets) is recommended for select patients with clinically relevant thrombocytopenia or neutropenia; or for select patients with symptomatic anemia.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Atgam. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Atgam as well as the monitoring required for adverse events and long-term efficacy, approval requires Atgam to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Atgam is recommended in those who meet one of the following criteria:

FDA-Approved Indications

100. Allograft Rejection in Solid Organ Transplant. Approve for 1 month if the patient meets the following (A and B):
- **A)** Patient meets ONE of the following (i or ii):
  - **i.** Atgam is used for induction therapy, prior to, at the time of, or immediately following transplantation; OR
  - **ii.** Atgam is used for the treatment of acute rejection; AND
- **B)** The medication is prescribed by or in consultation with a transplant specialist physician or a physician associated with a transplant center.

101. Aplastic Anemia. Approve for 1 month if the patient meets the following (A and B):
- **A)** Patient has moderate to severe disease; AND
- **B)** The medication is prescribed by or in consultation with a hematologist or a physician who specializes in the treatment of aplastic anemia.

Other Uses with Supportive Evidence

102. Hematopoietic Stem Cell Transplantation or Umbilical Cord Transplantation. Approve for 1 month if the patient meets the following (A and B):
- **A)** Atgam is used as part of a conditioning regimen beginning prior to hematopoietic stem cell transplantation or umbilical cord transplantation; AND
- **B)** The medication is prescribed by or consultation with an oncologist or a physician who specializes in stem cell or umbilical cord transplantation.

103. Graft-Versus-Host Disease. Approve for 1 month if the patient meets the following (A, B, and C):
- **A)** Patient has acute disease; AND
- **B)** Patient's disease is refractory or resistant to corticosteroid therapy; AND
- **C)** The medication is prescribed by or consultation with an oncologist or a physician who specializes in transplantation.

104. Immune Checkpoint Inhibitor-Related Toxicities. Approve for 1 month if the patient meets the following (A, B, C, and D):

A) Patient has received at least one immune checkpoint inhibitor; AND
Note: Immune checkpoint inhibitors include Opdivo (nivolumab intravenous infusion), Keytruda (pembrolizumab intravenous infusion), Tecentriq (atezolizumab intravenous infusion), Bavencio (avelumab intravenous infusion), Imfinzi (durvalumab intravenous infusion), Yervoy (ipilimumab intravenous infusion), Libtayo (cemiplimab intravenous infusion), Jemperli (dostarlimab intravenous infusion).

B) Patient meets ONE of the following (i or ii):

i. Patient has cardiac immune-related adverse events; OR
Note: Examples of cardiac immune-related adverse events are myocarditis, pericarditis, arrhythmias, impaired ventricular function, large vessel vasculitis.

ii. Patient has elevated liver enzymes or toxic liver disease; AND

C) Patient has not improved after therapy with corticosteroids; AND
Note: Examples of corticosteroids include prednisone, dexamethasone, methylprednisolone.

D) The medication is prescribed by or consultation with a cardiologist, oncologist, gastroenterologist, or a physician who specializes in the treatment of immune checkpoint inhibitor-related toxicity.

105. Myelodysplastic Syndrome. Approve for 1 month if the patient meets the following (A and B):

A) Patient has lower risk disease; AND
Note: Lower risk disease is defined as International Prognostic Scoring System (IPSS) risk of low or intermediate-1; IPSS-Revised (IPSS-R) risk of very low, low, or intermediate; IPSS-Molecular (IPSS-M) risk of very low, low, moderate low. Other risk stratification models may also be used (e.g., the MD Anderson Cancer Center or the World Health Organization Prognostic Scoring System).

B) The medication is prescribed by or in consultation with an oncologist or a physician who specialized in the treatment of myelodysplastic syndromes.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Atgam is not recommended in the following situations:

157. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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545. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 3.2023 – November 19, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed December 12, 2023.

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PRIOR AUTHORIZATION POLICY

POLICY: Immune Globulin Intravenous Prior Authorization Policy

- Asceniv™ (immune globulin intravenous solution-sira – ADMA Biologics)
- Bivigam® (immune globulin intravenous solution– AMDA Biologics)
- Flebogamma® DIF (immune globulin intravenous solution – Grifols)
- Gammagard Liquid (immune globulin solution – Takeda)
- Gammagard® S/D < 1 mcg/mL in 5% solution (immune globulin intravenous solution– Takeda)
- Gammaked™ (immune globulin solution caprylate/chromatography purified – Kedrion)
- Gammaplex® (immune globulin intravenous solution – BPL)
- Gamunex®-C (immune globulin solution caprylate/chromatography purified – Grifols)
- Octagam® (immune globulin intravenous solution– Octapharma)
- Panzyga® (immune globulin intravenous solution-ifas – Octapharma/Pfizer)
- Privigen® (immune globulin intravenous solution – CSL Behring)

REVIEW DATE: 10/25/2023

OVERVIEW

Immune globulin intravenous (IVIG) products are concentrated human immunoglobulins, primarily immunoglobulin G (IgG).

All of these products (except Octagam 10%) are FDA-approved for replacement therapy in patients with primary immune deficiencies due to defects in humoral immunity. The following indications are FDA-approved:

- **B-cell chronic lymphocytic leukemia (CLL)**, for prevention of bacterial infections in patients with hypogammaglobulinemia and/or recurrent bacterial infections.[6,18,21]
- **Chronic inflammatory demyelinating polyneuropathy,** to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.[7,9,12,67]
- **Dermatomyositis (or polymyositis).** Octagam 10% is indicated for the treatment of dermatomyositis in adults.[11] Patients with dermatomyositis treated with Octagam were under treatment with corticosteroids and/or maximally two immune-suppressants OR patients had previous failure or intolerance with a corticosteroid and at least one additional immunosuppressive drug.[33] IVIG may be considered amongst the treatment options for patients with polymyositis not responding to first line immunosuppressive treatment.[32]
- **Idiopathic (immune) thrombocytopenic purpura (ITP)**, acute and chronic, when a rapid rise in platelet count is needed to prevent and/or control bleeding or to allow a patient with ITP to undergo surgery.[2,4,6-9,11,12,15,23-25]
- **Kawasaki disease** in pediatric patients for the prevention of coronary artery aneurysm.[6,26]
- **Multifocal motor neuropathy** in adults as maintenance therapy to improve muscle strength and disability.[5]
- **Primary humoral immune deficiency (PID)**, for replacement therapy, including but not limited to the humoral immune defect in the following conditions: common variable immunodeficiency, X-linked agammaglobulinemia [congenital agammaglobulinemia], Wiskott-Aldrich Syndrome, and severe combined immunodeficiencies.[1-10,12,15,16,25] Gammagard Liquid 10%, Gammaked, and Gamunex-C may be administered via intravenous (IV) or subcutaneous infusion for primary immunodeficiency.[5,7,9] IVIG

is also indicated for measles prophylaxis in individuals with PID who have been exposed to measles or who are at high risk of measles exposure.[3,4,7-10,12,13,17,25,45]

IVIG is prepared from pooled plasma collected from a large number of human donors.[1-12,15,16,25] The donors in a typical pool of plasma have a wide range of antibodies against infectious agents. These products have IgG subclasses similar to that found in normal humans. Asceniv contains not only antibodies which satisfy the requirement to treat patients with PID, it also has elevated levels of respiratory syncytial virus (RSV) antibodies.[19]

IVIG also is used for many off-label indications. Much of the evidence for clinical effectiveness of IVIG is anecdotal (i.e., case reports, open series, or cohort studies). Some conditions have been studied in controlled trials. Usually IVIG is indicated only if standard approaches have failed, become intolerable, or are contraindicated.

- **Antibody-mediated rejection (AMBR) in transplantation:** Current strategies for treatment of antibody-mediated rejection include plasmapheresis, IVIG, and T-cell or B-cell-depleting agents.[75] Although there are no controlled trials regarding the most appropriate treatments, the benefits of immune globulin have been well described and has been used as the standard-of-care (along with plasmapheresis) in multiple studies.[18,76] Clinical practice guidelines (2009 Kidney Disease: Improving Global Outcomes) recommends a combination of corticosteroids, plasmapheresis, IVIG, anti-CD-20 antibody, and lymphocyte-depleting antibody for antibody-mediated rejection.[76,77] As in desensitization therapy, much of the information for IVIG use is in patients with kidney transplants, but the same principles apply to transplantation of other organs and tissues. Immune globulin has been used in lung transplant patients to treat ABMR[20,44,78] and a scientific statement from the American Heart Association states that primary therapy for ABMR in patients with heart transplants may include IVIG, plasmapheresis, high-dose corticosteroids, and anti-lymphocyte antibodies.[36]
- **Autoimmune mucocutaneous blistering diseases (pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid [cicatricial pemphigoid], and epidermolysis bullosa acquisita):** Conventional therapy (a systemic corticosteroid and an immunosuppressive agent) is started at the same time or before IVIG. Many case reports and uncontrolled case series suggest benefit of IVIG in patients with recalcitrant disease or in those with contraindications to conventional therapy.[28-30] International expert recommendations for the management of pemphigus note that first-line treatment includes corticosteroids and anti-CD20 monoclonal antibodies. First-line corticosteroid-sparing agents include azathioprine and mycophenolate mofetil, and other corticosteroid-sparing agents include IVIG.[2]
- **Cytomegalovirus (CMV) pneumonitis or pneumonia in patients with cancer or transplant-related infection:** For CMV pneumonia, therapy generally consists of antivirals (e.g., ganciclovir, foscarnet). The National Comprehensive Cancer Network (NCCN) guidelines on prevention and treatment of cancer-related infections (version 1.2023 – June 28, 2023) lists IVIG as an adjunctive therapy for CMV pneumonitis, but notes that IVIG use as an antiviral is controversial.[31]
- **Desensitization therapy prior to and immediately after transplantation:** Most of the information on use of IVIG for desensitization is in patients with kidney transplantation but many of the same principles apply to transplantation of other organs and tissues.[34,35] Current protocols include using low-dose IVIG with plasma exchange or high-dose IVIG with or without B-cell depletions with rituximab for IV infusion.[18]
- **Guillain Barré syndrome (GBS):** The American Academy of Neurology recommends IVIG in patients who require aid to walk within 2 or 4 weeks from the onset of neuropathic symptoms.[37] The effect of IVIG in GBS has only been investigated in randomized controlled trials in patients who are unable to walk at nadir (i.e., severely affected patients), not in mildly affected patients who are able to walk unaided at nadir.[38] IVIG is not indicated or proven to be effective in patients mildly affected with GBS.[32,38]

- **Hematologic neoplasm-associated hypogammaglobulinemia or hypogammaglobulinemia after B-cell targeted therapies (secondary immunodeficiency):** Clinical guidelines for immunoglobulin use by the National Health Service- England note secondary antibody deficiency can be hypogammaglobinemia associated with therapeutic monoclonals targeted at B-cells and plasma cells, non-Hodgkin's lymphoma, CLL, multiple myeloma, or other relevant B-cell malignancies.[27] NCCN guidelines regarding management of immunotherapy-related toxicities (version 2.2023 – May 9, 2023) recommends that after anti-CD19 chimeric antigen receptor (CAR)-T cell therapy, IVIG replacement should be considered for patients with serum IgG levels < 400 to 600 mg/dL and serious or recurrent infections.[73]
- **Hematopoietic cell transplantation (HCT) to prevent infections:** HCT is defined as transplantation of any blood- or marrow-derived hematopoietic stem cells, regardless of transplant type (i.e., allogeneic or autologous) or cell source (i.e., bone marrow, peripheral blood, or umbilical cord blood). With regard to IVIG, guidelines recommend IVIG for prevention or preemptive treatment of specific infections in HCT recipients.[39] In adult or adolescent HCT recipients (allogeneic or autologous), IVIG is used to prevent infections in those with severe hypogammaglobulinemia (i.e., serum IgG < 400 mg/dL) during the first 100 days after HCT. In pediatric patients, IVIG is indicated in those with an allogeneic HCT if hypogammaglobulinemia is severe during the first 100 days after HCT. For prevention of infections beyond 100 days post-HCT (allogeneic or autologous), IVIG is recommended in recipients with severe hypogammaglobulinemia (i.e., serum IgG < 400 mg/dL). NCCN guidelines on prevention and treatment of cancer-related infections discussed similar recommendations.[31]
- **Human Immunodeficiency virus (HIV)- or Hepatitis C-associated thrombocytopenia:** Secondary ITP can occur in patients with HIV infection.[23,24] It can also occur in patients with Hepatitis C. The American Society of Hematology (ASH) guidelines for ITP recommend initial treatment with corticosteroids, IVIG, or Rh0(D) immune globulin for patients with secondary ITP due to HIV. ASH also recommends IVIG for secondary ITP associated with Hepatitis C.[23,24]
- **HIV-infected infants and children to prevent recurrent infections:** IVIG is recommended to prevent serious bacterial infections in HIV-infected children who have hypogammaglobulinemia (IgG < 400 mg/dL).[40] Clinicians providing care for adolescents are advised to use the US Department of Health and Human Services Adult and Adolescent HIV-guideline for the care of post-pubertal adolescents (sexual maturity rating [SMR] 4 and 5) and to use the pediatric guideline for guidance on the care of adolescents at SMR 3 or lower.[40]
- **Immunotherapy-related toxicities associated with checkpoint inhibitor therapy:** NCCN guidelines for the management of immunotherapy-related toxicities (version 2.2023 – May 9, 2023) recommend IVIG for the management of severe pneumonitis after 48 hours of methylprednisolone therapy, as treatment for severe myasthenia gravis, encephalitis, cardiovascular adverse events, musculoskeletal adverse events, moderate or severe GBS, transverse myelitis, bullous dermatitis, and Stevens-Johnson syndrome/toxic epidermal necrolysis.[73] The American Society of Clinical Oncology also has practice guidelines on the management of immune-related adverse events in patients treated with checkpoint inhibitor therapy.[74] These practice guidelines address the above mentioned indications along with other conditions (e.g., severe cutaneous skin adverse reactions, myositis, autoimmune hemolytic anemia, immune thrombocytopenia).
- **Lambert-Eaton Myasthenic Syndrome:** Limited but moderate- to high-quality evidence from randomized controlled trials have shown that 3,4-diaminopyridine or IVIG was associated with improved muscle strength score and compounded muscle action potential amplitudes. IVIG may be used as an alternative in patients who do not respond or do not tolerate other therapies.[18]
- **Multiple myeloma:** Patients with multiple myeloma are often functionally hypogammaglobulinemic with total immunoglobulin production being elevated, but the repertoire of antibody production restricted.[31] The NCCN guidelines on multiple myeloma (version 1.2024 – September 22, 2023) notes that IVIG replacement during CAR-T cell and bispecific antibody therapies are not guided by the

presence of infections.[42] It also should be considered in the setting of recurrent, serious infections and/or hypogammaglobulinemia (IgG ≤ 400 mg/dL).

- **Multiple sclerosis, acute severe exacerbation or relapses:** Medication options for relapse management include high dose corticosteroids, intramuscular adrenocorticotrophic hormone, plasmapheresis, and IVIG. IVIG is sometimes used to treat relapses that do not respond to corticosteroids.[43] During pregnancy, relapses severe enough to require treatment can be safely managed with a short-term course of corticosteroids after the first trimester. Methylprednisolone is the preferred agent because it is metabolized before crossing the placenta.[43]
- **Myasthenia gravis:** Recommendations from an international consensus guidance statement for management of adult or juvenile myasthenia gravis include the use of IVIG in some patients.[65] Symptomatic and immunosuppressive treatment of myasthenia gravis includes pyridostigmine as initial therapy in most patients. Corticosteroids or immunosuppressive therapies are used in all patients with myasthenia gravis who have not met treatment goals after an adequate trial of pyridostigmine. A nonsteroidal immunosuppressive agent (e.g., azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus) should be used alone when corticosteroids are contraindicated or refused. In patients with refractory myasthenia gravis, chronic IVIG and chronic plasma exchange (PLEX), cyclophosphamide, or rituximab may be used. PLEX and IVIG are recommended as short-term treatments in patients with myasthenia gravis with life-threatening effects such as respiratory insufficiency or dysphagia, to prepare for surgery in patients with significant bulbar dysfunction, when rapid response is needed, when other treatments are not adequate, and before starting corticosteroids if necessary to prevent or minimize exacerbations. IVIG can be considered as maintenance therapy in patients with refractory myasthenia gravis or in patients with relative contraindications to immunosuppressive agents. Refractory myasthenia gravis is defined as the post intervention status of unchanged or worse after corticosteroids and at least two other immunosuppressive agents used in adequate doses for an adequate duration, with persistent symptoms or side effects that limit functioning as defined by the patient or physician.
- **Passive immunization for measles (post-exposure prophylaxis):** When administered within 6 days of exposure, immune globulin (IG) can prevent or modify measles in patients who are nonimmune.[13] IG therapy is not indicated in persons who have received one dose of measles-containing vaccine at ≥ 12 months, unless the patient is severely immunocompromised. The Advisory Committee on Immunization Practices recommends the use of IG therapy for post-exposure prophylaxis of measles in the following patients who are at risk for severe disease and complication from measles: infants < 12 months of age, pregnant women without evidence of measles immunity, and severely immunocompromised persons.[13] For infants < 12 months of age, intramuscular IG is used; infants 6 through 11 months of age can receive measles, mumps, and rubella vaccine instead of IG if given within 72 hours of exposure. IVIG is used for pregnant women and severely immunocompromised patients.
- **Post-exposure prophylaxis for varicella OR treatment or post-exposure prophylaxis for tetanus:** Children infected with HIV without a history of previous varicella infection OR children who have not received two doses of varicella vaccine should receive VariZIG or, if not available, IVIG within 10 days after close contact with a person who has chickenpox or shingles.[41,46] VariZIG is indicated for post-exposure prophylaxis in certain patients without immunity to varicella and is given as soon as possible after exposure, preferably within 4 days, and as late as 10 days after exposure.[47] Per the Centers for Disease Control and Prevention, if tetanus immune globulin is not available, clinicians can use immune globulin at a dose of 200 to 400 mg/kg.[48]
- **Parvovirus B19 infection and pure red blood cell aplasia, immunologic subtype:** In immunosuppressed patients lacking neutralizing antibodies, IVIG has been useful for the treatment of persistent B19 infection.[49] The guidelines from the American Society of Transplantation Infectious Diseases Community of Practice state that IVIG is frequently used for the treatment of solid organ transplant recipients with symptomatic parvovirus B19 infection.[66] A Canadian expert panel of hematologists recommend prednisone followed by cyclophosphamide or cyclosporine as first-line

therapy for immunologic type pure red blood cell aplasia.[22] The panel considers IVIG a reasonable second-line option for this serious condition.

- **Stiff-Person Syndrome (Moersch-Woltman Syndrome):** Per the European Federation of Neurological Societies, IVIG should be reserved for patients who have no symptomatic relief after the use of diazepam and/or baclofen and have severe disability in carrying out daily activities.[32]
- **Thrombocytopenia, feto-neonatal alloimmune:** Antenatal therapy with IVIG administered to the mother is effective in increasing fetal platelet counts in neonatal alloimmune thrombocytopenia.[50,51] First-line therapy for newborns with fetal/neonatal alloimmune thrombocytopenia is antigen-negative compatible platelets; IVIG is adjunctive therapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of IVIG products. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with IVIG as well as the monitoring required for adverse events and long term efficacy, initial approval requires IVIG products to be prescribed by or in consultation with a physician who specialized in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of immune globulin intravenous products is recommended in those who meet one of the following criteria:

FDA-Approved Indications

106. Primary Immunodeficiencies. Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient meets ONE of the following (a, b, or c):

Note: An exception can be made for the impaired antibody response if, according to the prescriber, the delay caused by pre-vaccination and post-vaccination antibody measurement would be deleterious to the patient's health.

a) Patient has a diagnosis of congenital agammaglobulinemia, X-linked agammaglobulinemia, other agammaglobulinemia due to the absence of B-cells, Wiskott-Aldrich syndrome, ataxia telangiectasia, DiGeorge syndrome, severe combined immunodeficiency, Hyper-Immunoglobulin M (IgM) syndromes, an IgG level lower than 250 mg/dL, or a primary immune deficiency which has been confirmed by genetic or molecular testing; OR

b) Patient has a diagnosis of common variable immunodeficiency, unspecified hypogammaglobulinemia, or other immunodeficiencies with significant hypogammaglobulinemia and meets BOTH of the following (1 and 2):

(1) Patient's pretreatment IgG level is below the normal range (age-adjusted and according to the normal reference range for the reporting laboratory); AND

(2) Patient meets ONE of the following [(a) or (b)]:

(i) Patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens); OR

Note: An exception can be made for the impaired antibody response if, according to the prescriber, the delay caused by pre-vaccination and post-vaccination antibody measurement would be deleterious to the patient's health.

(ii) Patient has recurrent infections; OR

c) Patient has an IgG subclass deficiency, selective antibody deficiency (SAD), or another confirmed primary immunodeficiency and meets the following criteria (1 and 2):

(1) Patient has an impaired antibody response (i.e., failure to product antibodies to specific antigens); AND

(2) Patient has recurrent infections; AND

ii. The medication is prescribed by or in consultation with one of the following physician specialists: an allergist, immunologist, otolaryngologist (ear nose and throat [ENT] physician), pulmonologist, or an infectious diseases physician who treats patients with primary immune deficiencies.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has been diagnosed with a primary immunodeficiency and, according to the prescriber, is continuing to receive benefit from the product.

Note: Examples of continued benefit with the product includes increased IgG levels or prevention and/or controlling of infections.

107. B-Cell Chronic Lymphocytic Leukemia for Prevention of Infections. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets BOTH of the following (i and ii):

i. Patient meets ONE of the following (a or b):

a) Patient has an immunoglobulin G (IgG) level < 600 mg/dL (6.0 g/L); OR

b) Patient has a history of recurrent infections; AND

ii. The medication is prescribed by or in consultation with an oncologist, hematologist, or infectious diseases physician.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has a positive response to therapy according to the prescriber.

Note: Examples of a positive response to therapy include maintaining an increased IgG trough level or a decrease in the number of infections.

108. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or Polyradiculoneuropathy. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii)

i. Electrodiagnostic studies support the diagnosis of CIDP; AND

ii. The medication is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has a clinically significant improvement in neurologic symptoms, as determined by the prescriber.

Note: Examples of improvement in neurologic symptoms include improvement in disability; nerve conduction study results improved or stabilized; physical examination show improvement in neurological symptoms, strength, and sensation.

109. Dermatomyositis or Polymyositis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, and iv):

i. Prior to starting any therapy for this condition, the patient meets one of the following (a or b):

a) Patient has or had an elevated creatinine kinase (CK) level, according to the prescriber; OR

b) Other measures support the diagnosis, according to the prescriber, including, but not limited to, skin manifestations, autoantibody testing, muscle biopsy results, electromyographic (EMG) findings; AND

ii. Patient has tried a systemic corticosteroid OR a corticosteroid is contraindicated according to the prescriber; AND

iii. Patient has tried an immunosuppressive agent OR an immunosuppressive agent is contraindicated according to the prescriber; AND

Note: Examples of immunosuppressive agents include azathioprine, methotrexate, cyclosporine, cyclophosphamide, and mycophenolate mofetil.

iv. The medication is prescribed by or in consultation with a neurologist or rheumatologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has responded to therapy according to the prescriber.

Note: Examples of a response to therapy includes improved muscle strength, improved neuromuscular symptoms, and improved functional ability.

110. Immune Thrombocytopenia (ITP). Approve for the duration noted if the patient meets ONE of the following (A, B, C, D, or E):

Note: The diagnosis of ITP encompasses previous nomenclature, such as idiopathic thrombocytopenia, idiopathic thrombocytopenic purpura, immune thrombocytopenic purpura.

A) Initial Therapy – Adult ≥ 18 Years of Age. Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):

i. Patient meets ONE of the following (a, b, or c):

a) Patient has tried a systemic corticosteroid (e.g., prednisone); OR

b) There is an urgent need to increase the platelet count quickly; OR

c) A systemic corticosteroid is contraindicated according to the prescriber; AND

ii. The medication is prescribed by or in consultation with a hematologist.

B) Initial Therapy – Patient is < 18 Years of Age. Approve for 1 year if prescribed by or in consultation with a hematologist.

C) Initial Therapy – To Increase Platelet Count Before Surgical or Dental Procedures: Approve for 1 month if prescribed by or in consultation with a hematologist.

D) Initial Therapy – Pregnant Patient. Approve for 6 months if prescribed by or in consultation with a hematologist.

E) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has responded to therapy according to the prescriber.

Note: Examples of responding to therapy include increased platelet counts, absence of significant bleeding, or preventing hemorrhage/ensuring an adequate platelet count in order for delivery in pregnant patients.

111. Kawasaki Disease. Approve for 3 months if prescribed by or in consultation with a pediatric cardiologist or a pediatric infectious diseases physician.

112. Multifocal Motor Neuropathy. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. The diagnosis is supported by weakness without sensory abnormalities, upper motor neuron signs, or marked bulbar involvement and meets ONE of the following (a, b, or c):

a) The diagnosis is supported by nerve conduction studies that demonstrate motor conduction block or probably motor conduction block; OR

b) The prescriber has determined the patient has multifocal motor neuropathy without conduction block; OR

c) The diagnosis if supported by a motor nerve biopsy or by a magnetic resonance imaging (MRI) neurography; AND

ii. The medication is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has improvement in neurologic symptoms as determined by the prescriber.

Note: Examples of improvement in neurologic symptoms include improvement in disability, grip strength improvement (measured with dynamometer), physical examination show improvement in neurological symptoms and strength.

Other Uses with Supportive Evidence

113. Antibody-Mediated Rejection in Transplantation. Approve for 1 year if prescribed by or in consultation with a physician affiliated with a transplant center.

114. Autoimmune Mucocutaneous Blistering Diseases (Pemphigus Vulgaris, Pemphigus Foliaceus, Bullous Pemphigoid, Mucous Membrane Pemphigoid [Cicatricial Pemphigoid], and Epidermolysis Bullosa Acquisita). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient meets ONE of the following (a, b, or c):

a) Patient meets BOTH of the following (1 and 2):

(1) Patient has tried a systemic corticosteroid OR a corticosteroid is contraindicated according to the prescriber; AND

(2) Patient has tried an immunosuppressive agent OR an immunosuppressive agent is contraindicated according to the prescriber; OR

Note: Examples of immunosuppressive agents include azathioprine, cyclophosphamide, dapsone, methotrexate, cyclosporine, mycophenolate mofetil, and tacrolimus.

b) Patient has rapid, debilitating, progressive disease, that cannot be controlled with a systemic corticosteroid and an immunosuppressive agent; OR

c) The disease is so serious that there is inadequate time for therapy with a systemic corticosteroid and an immunosuppressive agent to have a rapid enough effect; AND

ii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has responded to therapy according to the prescriber.

Note: Examples of response to therapy can include healing of previous lesions or fewer new lesions.

115. Cytomegalovirus Pneumonitis or Pneumonia in Patients with Cancer or Transplant-Related Infection. Approve for 2 months if prescribed by or in consultation with an oncologist, hematologist, or an infectious diseases physician.

116. Desensitization Therapy Prior to and Immediately after Transplantation. Approve for 1 year if prescribed by or in consultation with a physician affiliated with a transplant center.

117. Guillain Barré Syndrome. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month (this is to provide one course of therapy) if the patient meets BOTH of the following (i and ii):

i. Patient meets ONE of the following (a or b):

a) The medication is initiated within 2 weeks and no longer than 4 weeks of onset of neuropathic symptoms; OR
Note: Examples of neuropathic symptoms include weakness, inability to stand or walk without assistance, and respiratory or bulbar weakness.
b) Patient has had a relapse (treatment related fluctuation), but had an initial response to IVIG; AND

ii. The medication is prescribed by or in consultation with a neurologist or a specialist with experience in diagnosing and treating patients with Guillain Barr**é** Syndrome.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 month (this is to provide a second course) about 3 weeks after the first course.

118. Hematologic Neoplasm-Associated Hypogammaglobulinemia or Hypogammaglobulinemia after B-cell Targeted Therapies (Secondary Immunodeficiency). Approve for 6 months if the patient meets ONE of the following (A or B):
Note: Some examples of B-cell targeted therapy are chimeric antigen receptor (CAR)-T cell therapy (e.g., Kymriah [tisagenlecleucel intravenous infusion], Abecma [idecabtagene vicleucel intravenous infusion], Breyanzi [lisocabtagene maraleucel intravenous infusion], Tecartus [brexucabtagene autoleucel intravenous infusion], Yescarta [axicabtagene ciloleucel intravenous infusion]), a rituximab product, Besponsa (inotuzumab ozogamicin intravenous infusion).
Note: Refer to B-Cell Chronic Lymphocytic Leukemia (CLL) for Prevention of Infections and Multiple Myeloma for diagnosis-specific criteria.

A) Initial Therapy. Approve if the patient meets ALL of the following (i, ii, and iii):

i. Patient has an immunoglobulin G (IgG) level of < 600 mg/dL (6.0 g/L) [excluding paraprotein]; AND

ii. Patient has recurrent or severe infections or there is a high risk of infection, according to the prescriber; AND

iii. The medication is being prescribed by or in consultation with an oncologist, hematologist, infectious diseases physician, or immunologist.

B) Patient is Currently Receiving Immune Globulin. Approve if the patient is having a positive response to therapy according to the prescriber.
Note: Examples of a positive response to therapy include maintaining an increased IgG trough level or a decrease in the number of infections.

119. Hematopoietic Cell Transplantation (HCT) to Prevent Infection. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, iii, and iv):

i. Patient has had a HCT within the previous year; AND

ii. Patient has an immunoglobulin G (IgG) level < 600 mg/dL (6.0 g/L) OR the patient has multiple myeloma or malignant macroglobulinemia; AND

iii. According to the prescriber the patient has a significant risk of having frequent and/or severe infections; AND

iv. The medication is prescribed by or in consultation with a hematologist, oncologist, or infectious diseases physician.

B) Patient is Currently Receiving Immune Globulin. Approve for 6 months if the patient is having a positive response to therapy according to the prescriber.
Note: Examples of a positive response to therapy include maintaining an increased IgG trough level, controlling the number of infections, or a decrease in the number of infections.

120. Human Immunodeficiency Virus (HIV)- or Hepatitis C-Associated Thrombocytopenia. Approve for 1 month if the patient meets BOTH of the following (A and B):

A) Patient is receiving antiviral therapy; AND

B) The medication is prescribed by or in consultation with an infectious diseases specialist, a physician who specializes in the treatment of HIV infections, a gastroenterologist, hepatologist, or a liver transplant physician.

121. Human Immunodeficiency Virus (HIV), to Prevent Recurrent Infections. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, and iv):

i. Patient is < 18 years of age; AND

ii. Patient is receiving combination antiretroviral therapy; AND

iii. Patient has ONE of the following (a, b, or c):

a) Hypogammaglobulinemia (i.e., IgG < 400 mg/dL [4.0 g/L]); OR

b) Functional antibody deficiency is demonstrated by poor specific antibody titers (that is, the patient does not develop specific antibody responses against protein and polysaccharide antigens); OR

c) Functional antibody deficiency is demonstrated by the patient having recurrent (two or more per year), serious infections (e.g., bacteremia, meningitis, pneumonia) despite administration of combination antiretroviral therapy and appropriate antimicrobial prophylaxis; AND

iv. The medication is prescribed by or in consultation with an infectious diseases specialist or an immunologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the frequency and/or severity of infections have decreased according to the prescriber.

122. Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy. Approve for the duration noted if the patient meets ONE of the following (A or B):

Note: Examples of checkpoint inhibitors are: Keytruda (pembrolizumab intravenous infusion), Opdivo (nivolumab intravenous infusion), Yervoy (ipilimumab intravenous infusion), Tecentriq (atezolizumab intravenous infusion), Bavencio (avelumab intravenous infusion), Imfinzi (durvalumab intravenous infusion), Libtayo (cemiplimab intravenous infusion), Jemperli (dostarlimab intravenous infusion).

A) Initial Therapy. Approve for 1 month if the patient meets ONE of the following (i, ii, or iii):

i. Patient has tried a systemic corticosteroid and has not adequately responded to therapy; OR
Note: Examples of systemic corticosteroids include prednisone, methylprednisolone.

ii. The medication is being started with a systemic corticosteroid; OR

iii. A corticosteroid is contraindicated per the prescriber.

B) Patient is Currently Receiving Immune Globulin. Approve for 6 months if the patient is having a positive response to therapy, as determined by the prescriber, and the prescriber has determined extended therapy is required.

123. Lambert-Eaton Myasthenic Syndrome (LEMS). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month (to allow for one course of therapy) if the patient meets ALL of the following (i, ii, and iii):

i. Patient is having refractory weakness after symptomatic treatment of LEMS with an amifampridine product (e.g., Firdapse, Ruzurgi), guanidine, or pyridostigmine; AND

ii. Patient meets ONE of the following (a or b):

a) Patient has paraneoplastic LEMS; OR

b) Patient has non-paraneoplastic LEMS AND has tried a systemic corticosteroid (e.g., prednisone) or another immunosuppressive agent (e.g., azathioprine), or has a

contraindication to corticosteroids and/or immunosuppressive agents, according to the prescriber; AND

iii. The medication is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has a response or continued effectiveness, according to the prescriber.

Note: Examples of a response to therapy include improved muscle strength or other clinical response.

124. Multiple Myeloma. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient meets ONE of the following (a or b):

a) Patient has or is at risk of severe recurrent infections according to the prescriber; OR

b) Patient will be starting, has taken, or is currently receiving chimeric antigen receptor (CAR)-T cell therapy OR bispecific antibody therapy; AND

Note: Examples of CAR-T cell therapy includes: Abecma (idecabtagene vicleucel intravenous infusion), Carvykti (ciltacabtagene autoleucel infusion).

Note: Examples of bispecific antibody therapy includes: Elrexfio (elranatamab-bcmm subcutaneous injection), Tecvayli (teclistamab-cqyv subcutaneous injection), Talvey (talquetamab-tgvs subcutaneous injection).

ii. The medication is prescribed by or in consultation with a hematologist, oncologist, or infectious diseases specialist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year.

125. Multiple Sclerosis (MS), Acute Severe Exacerbation or Relapses. Approve for 1 month (this is to provide one course of therapy) if the patient meets ALL of the following (A, B, and C):

A) The patient meets ONE of the following (i or ii):

i. Patient has either not responded to or has had a significant adverse reaction with systemic corticosteroids (e.g., methylprednisolone sodium succinate injection) OR plasma exchange; OR

Note: A trial of Acthar H.P. gel [repository corticotropin injection; adrenocorticotropic hormone, ACTH] would also count toward meeting this requirement.

ii. A systemic corticosteroid is contraindicated according to the prescriber; AND

B) Patient meets ONE of the following (i or ii):

i. Patient is already on maintenance therapy for MS or will be starting maintenance therapy for MS; OR

Note: Maintenance therapy does NOT include IVIG. Examples of maintenance therapy for MS would include: Avonex (interferon beta-1a injection), Plegridy (peginterferon beta-1a injection), Rebif (interferon beta-1a injection), Betaseron (interferon beta-1b injection)/Extavia (interferon beta-1b injection), Copaxone (glatiramer injection)/Glatopa (glatiramer injection), Gilenya (fingolimod capsule), Lemtrada (alemtuzumab injection), Aubagio (teriflunomide tablet), Mavenclad (cladribine tablet), Mayzent (siponimod tablet), Tecfidera (dimethyl fumarate capsule), Vumerity (diroximel fumarate capsule), Zeposia (ozanimod capsule), Tysabri (natalizumab injection), Novantrone (mitoxantrone injection), Bafiertam (monomethyl fumarate capsule), Kesimpta (ofatumumab injection), Ocrevus (ocrelizumab injection), Ponvory (penesimod tablet).

ii. Patient is pregnant or patient is post-partum and the prescriber has determined maintenance therapy is not clinically appropriate.

C) The medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of MS.

126. Myasthenia Gravis. Approve for the duration noted if the patient meets ONE of the following (A, B, C, or D):

A) Initial Therapy for Short-Term (Acute) Use. Approve for 5 days (to allow for one course of therapy) if the patient meets BOTH of the following (i and ii):

i. The patient meets ONE of the following conditions (a, b, c, or d):

a) The patient has an exacerbation of myasthenia gravis; OR

b) The patient requires stabilization of myasthenia gravis before surgery; OR

c) The patient has been started on an immunosuppressive drug and is waiting for full effect; OR

Note: Examples of immunosuppressive drugs include azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, methotrexate, or tacrolimus.

d) The patient is starting therapy with a corticosteroid and IVIG is being given to prevent or minimize exacerbations; AND

ii. The medication is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Immune Globulin Short-Term (Acute) Use. Approve for 5 days (to allow for one course of therapy).

C) Initial Therapy for Maintenance. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, and iv):

i. The patient has refractory myasthenia gravis; AND

ii. The patient has tried pyridostigmine; AND

iii. The patient has tried immunosuppressive therapy with at least one of the following agents: azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, methotrexate, tacrolimus AND has had an inadequate response; AND

iv. The medication is prescribed by or in consultation with a neurologist.

D) Patient is Currently Receiving Immune Globulin for Maintenance Therapy. Approve for 1 year if the patient is responding according to the prescriber.

Note: Examples of responding to therapy includes improvement in weakness (bulbar, limb, or respiratory), improvement with ocular symptoms.

127. Passive Immunization for Measles (Post-Exposure Prophylaxis). Approve for 1 day (to allow for a single dose) if the patient meets ONE of the following (A or B):

Note: For patients with primary immune deficiency, see criteria for PID.

A) Patient is pregnant and meets BOTH of the following criteria (i and ii):

i. Patient has been exposed to measles; AND

ii. The patient does not have evidence of immunity to measles (i.e., the patient does not have a of the disease or age-appropriate vaccination); OR

B) Patient meets BOTH of the following criteria (i and ii):

i. Patient is immunocompromised; AND

ii. Patient has been exposed to measles.

128. Post-Exposure Prophylaxis for Varicella OR Treatment or Post-Exposure Prophylaxis for Tetanus. Approve for 1 day (to allow for a single dose) if the patient meets ONE of the following (A or B):

A) For Varicella post-exposure, Varicella immune globulin is not available or cannot be administered within 10 days of exposure; OR

B) For Tetanus treatment or post-exposure, Tetanus Immune globulin is not available.

129. Parvovirus B19 Infection. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 2 months if the patient meets BOTH of the following (i and ii):
- **i.** Patient has an immunodeficiency condition; AND
  Note: Examples of an immunodeficiency condition include patients with HIV infection, solid organ transplants (e.g., renal, liver), chemotherapy for hematologic malignancy.
- **ii.** The medication is prescribed by or in consultation with an infectious diseases specialist, immunologist, hematologist, or transplant specialist.

B) Patient is Currently Receiving Immune Globulin. Approve for 6 months.

130. Pure Red Blood Cell Aplasia (PRCA), Immunologic Subtype. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient has tried a systemic corticosteroid (e.g., prednisone); AND
- **ii.** Patient has tried either cyclophosphamide or cyclosporine; AND
- **iii.** The medication is prescribed by or in consultation with an infectious diseases specialist, immunologist, hematologist, or transplant specialist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 month if the patient has responded with an increase in hemoglobin and reticulocytosis, according to the prescriber.

131. Stiff-Person Syndrome (Moersch-Woltman Syndrome). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii):
- **i.** Patient meets ONE of the following (a or b):
  - **a)** Patient has tried a benzodiazepine (e.g., diazepam) or baclofen; OR
  - **b)** Patient has contraindications to both a benzodiazepine AND baclofen according to the prescriber; AND
- **ii.** The medication is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has responded to therapy according to the prescriber.
Note: Examples of response to therapy includes reduced stiffness or frequency of spasms, ability to walk unassisted.

132. Thrombocytopenia, Feto-neonatal Alloimmune. Approve for 6 months if the pregnant mother or newborn patient is prescribed the medication by or in consultation with a hematologist or an obstetrician.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of immune globulin intravenous is not recommended in the following situations:

158. Adrenoleukodystrophy. Evidence does not support IVIG use.[18]

159. Alzheimer's Disease (AD). In one multicenter, double-blind, Phase III, placebo-controlled trial, 390 patients with mild to moderate AD were randomized to therapy with IVIG 400 mg/kg or 200 mg/kg, or to placebo given every 2 weeks for 18 months.[61] There was no statistically significant difference in the rate of cognitive decline when compared to placebo. Also, there was not a statistically significant change in functional ability when compared to placebo. Large placebo-controlled trials with a longer observation period are needed to established efficacy, determine the optimal dose regimen, and to confirm the safety of IVIG in the general AD poputation.[52,53]

160. Amyotrophic Lateral Sclerosis. There is insufficient evidence to recommend IVIG.[18]

161. Asthma. Global Initiative for Asthma (GINA) guidelines for asthma management and prevention do not include recommendations for use of IVIG.[54]

162. Atopic Dermatitis. Limited data exist to determine the utility of IVIG in the management of atopic dermatitis.[55]

163. Autism. Evidence does not support IVIG use.[18] Well-controlled, double-blind trials are needed.

164. Chronic Fatigue Syndrome. Evidence does not support IVIG use.[56] One randomized, placebo-controlled trial did not find benefits in quality of life measures nor the Profile of Mood States for IVIG.[56] Although scores were improved in IVIG and placebo treatment groups, no significant between group differences was demonstrated.

165. Complex Regional Pain Syndrome (Reflex Sympathetic Dystrophy). There is insufficient evidence to recommend IVIG. In one single center study a single dose of 0.5 g/kg of IVIG produced a decrease in pain intensity by 50% or more compared to placebo in 3 of 12 patients.[57] In a randomized, placebo-controlled, multicenter trial, low-dose immunoglobulin treatment for 6 weeks was not effective in relieving pain in patients with moderate-to-severe complex regional pain syndrome.[58] Well-controlled large-scale trials are needed.

166. Crohn's Disease. There is insufficient evidence to recommend IVIG. In one single center case collection report, 19 patients with acute Crohn's disease (Crohn's Disease Activity Index [CDAI] 284.1 ± 149.8) who were resistant to steroids received IVIG daily for 7 to 10 days.[59] Four weeks after completing therapy, 14 patients were in clinical remission (CDAI < 150). Prospective, randomized, placebo-controlled trials are needed to determine if IVIG has a role in the treatment of Crohn's disease.

167. Cystic Fibrosis. There is insufficient evidence to recommend IVIG. In one single-center retrospective case review of 16 children with cystic fibrosis, IVIG was reportedly effective.[60] Well-designed, controlled trials are needed.[18]

168. Diabetes Mellitus, Immunotherapy. Evidence does not support IVIG use.[18,62,63] In one 2-year randomized controlled trial, IVIG was given every 2 months to children and adults with type 1 diabetes.[62] No beneficial effect was shown with IVIG compared with control and the authors concluded that IVIG therapy is unlikely to be a viable option for immunotherapy.

169. Fibromyalgia Syndrome. There is insufficient evidence to recommend IVIG. In one open-label single center study, 15 patients with fibromyalgia syndrome and distal demyelinating polyneuropathy received IVIG 400 mg/kg given daily for 5 days.[64] Pain, tenderness, and strength reportedly improved. Double-blind, placebo controlled trials are needed to determine if IVIG is effective in fibromyalgia syndrome.

170. In Vitro Fertilization (IVF). There is insufficient evidence to recommend IVIG administration as part of IVF outcomes.[68]

171. Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes (POEMS) Syndrome. Evidence does not support IVIG use.[18]

172. Recurrent Spontaneous Pregnancy Loss (RSPL) [Including a Patient with Antiphospholipid Antibody-Positive]. Evidence does not support IVIG use.[69-72] In one double-blind pilot study, IVIG

did not improve obstetric or neonatal outcomes beyond those achieved with a heparin and low-dose aspirin regimen.[69] In another double-blind trial (n = 82 of whom 47 had an index pregnancy), live birth rates did not differ significantly between IVIG-treated and placebo-treated women.[70] The American Society for Reproductive Medicine practice committee states that several trials and meta-analyses concluded that IVIG is ineffective for primary recurrent pregnancy loss and this treatment is not recommended.[72]

173. Selective Immune Globulin A (IgA) Deficiency as the Sole Immunologic Abnormality. Evidence does not support use of IVIG.[14,18] Selective IgA deficiency is defined as a serum IgA level less than 0.07 g/L, but normal serum IgG and IgM levels in a patient greater than 4 years of age in whom other causes of hypogammaglobulinemia have been excluded.[14] Selective IgA deficiency may co-exist in some patients with poor specific IgG antibody production, with or without IgG2 subclass deficiency.[14,18] Some of these patients with a concomitant specific antibody defect might benefit from therapy with IVIG.

174. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Immune Globulin Subcutaneous Prior Authorization Policy

- Cutaquig® (immune globulin 16.5% subcutaneous solution – Octapharma/Pfizer)
- Cuvitru™ (immune globulin 20% subcutaneous solution – Takeda)
- Gammagard Liquid (immune globulin 10% solution – Takeda)
- Gammaked™ (immune globulin 10% solution caprylate/chromatography purified – Kedrion)
- Gamunex®-C (immune globulin 10% solution caprylate/chromatography purified – Grifols)
- Hizentra® (immune globulin 20% subcutaneous solution – CSL Behring)
- HyQvia® (immune globulin 10% subcutaneous solution with recombinant human hyaluronidase – Takeda)
- Xembify® (immune globulin 20 % subcutaneous solution – Grifols)

REVIEW DATE: 10/25/2023

OVERVIEW

Immune globulin subcutaneous (SCIG) products are concentrated human immunoglobulins, primarily immunoglobulin G (IgG), that are prepared from pooled plasma collected from a large number of human donors. SCIG products are indicated for the following uses:

- **Chronic inflammatory demyelinating polyneuropathy**, for maintenance therapy in adults.[4]
- **Primary humoral immune deficiency (PID),** for replacement therapy, including but is not limited to the humoral defect in the following conditions: common variable immunodeficiency, X-linked agammaglobulinemia (congenital agammaglobulinemia), Wiskott-Aldrich syndrome, and severe combined immunodeficiencies (SCID).[1-5,7-9] SCIG is also indicated for measles prophylaxis in individuals with PID who have been exposed to measles or who are at high risk of measles exposure.[1,4,5,8,9]

Hizentra, Cuvitru, Xembify, and Cutaquig are indicated as a subcutaneous (SC) infusion only.[4,7-9] Gammagard Liquid, Gammaked, and Gamunex-C may be administered as a SC infusion or an intravenous infusion for PID.[1-3] HyQvia is indicated for SC infusion only, with sequential infusion of the recombinant human hyaluronidase first and followed 10 minutes later with the immune globulin infusion.[5] The recombinant human hyaluronidase acts locally to increase dispersion and absorption of the immune globulin. HyQvia has a Limitation of Use that the safety and efficacy of chronic use of recombinant human hyaluronidase in HyQvia have not been established in conditions other than PID.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of SCIG products. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with SCIG as well as the monitoring required for adverse events and long-term efficacy, initial approval requires SCIG products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Cutaquig, Cuvitru, Gammagard Liquid, Gammaked, Gamunex-C, Hizentra, and Xembify (all listed products except HyQvia) is recommended in those who meet the following criteria:

FDA-Approved Indications

133. Primary Immunodeficiencies. Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets BOTH of the following (i and ii):

i. Patient meets ONE of the following (a, b, or c):

Note: An exception can be made for the impaired antibody response if, according to the prescriber, the delay caused by pre-vaccination and post-vaccination antibody measurement would be deleterious to the patient's health.

a) Patient has a diagnosis of congenital agammaglobulinemia, X-linked agammaglobulinemia, other agammaglobulinemia due to the absence of B-cells, Wiskott-Aldrich syndrome, ataxia telangiectasia, DiGeorge syndrome, severe combined immunodeficiency, Hyper-Immunoglobulin M (IgM) syndromes, an IgG level lower than 250 mg/dL, or a primary immune deficiency which has been confirmed by genetic or molecular testing; OR

b) Patient has a diagnosis of common variable immunodeficiency, unspecified hypogammaglobulinemia, or other immunodeficiencies with significant hypogammaglobulinemia and meets the following [(1) and (2)]:

(1) Patient's pretreatment IgG level is below the normal range (age-adjusted and according to the normal reference range for the reporting laboratory); AND

(2) Patient meets ONE of the following [(a) or (b)]:

(i) Patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens); OR

(ii) Patient has recurrent infections; OR

c) Patient has an IgG subclass deficiency, selective antibody deficiency (SAD), or another confirmed primary immunodeficiency and meets the following [(1) and (2)]:

(1) Patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens); AND

(2) Patient has recurrent infections; AND

ii. The medication is prescribed by or in consultation with one of the following physician specialists: an allergist, immunologist, otolaryngologist (ear nose and throat [ENT] physician), pulmonologist, or an infectious diseases physician who treats patients with primary immune deficiencies.

B) Patient is Currently Receiving Immune Globulin. Approve if the patient has been diagnosed with a primary immunodeficiency and according to the prescriber the patient is continuing to receive benefit from the product.

Note: Examples of continued benefit with the product includes increased IgG levels or prevention and/or controlling of infections.

134. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or Polyradiculoneuropathy. Approve for the duration noted if the patient meets ONE the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):

i. The patient is ≥ 18 years of age; AND

ii. Electrodiagnostic studies support the diagnosis of CIDP; AND

iii. The medication has been prescribed by or in consultation with a neurologist; AND

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has a clinically significant improvement in neurologic symptoms, as determined by the prescriber.

Note: Examples of improvement in neurologic symptoms include improvement in disability; nerve conduction study results improved or stabilized; physical examination show improvement in neurological symptoms, strength, and sensation.

II. Coverage of HyQvia is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Primary Immunodeficiencies.** Approve for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets BOTH of the following (i and ii):
     - **i.** Patient meets ONE of the following (a, b, or c):
       Note: An exception can be made for the impaired antibody response if, according to the prescriber, the delay caused by pre-vaccination and post-vaccination antibody measurement would be deleterious to the patient's health.
       - **a)** Patient has a diagnosis of congenital agammaglobulinemia, X-linked agammaglobulinemia, other agammaglobulinemia due to the absence of B-cells, Wiskott-Aldrich syndrome, ataxia telangiectasia, DiGeorge syndrome, severe combined immunodeficiency, Hyper-Immunoglobulin M (IgM) syndromes, an IgG level lower than 250 mg/dL, or a primary immune deficiency which has been confirmed by genetic or molecular testing; OR
       - **b)** Patient has a diagnosis of common variable immunodeficiency, unspecified hypogammaglobulinemia, or other immunodeficiencies with significant hypogammaglobulinemia and meets the following [(1) and (2)]:
         - **(1)** Patient's pretreatment IgG level is below the normal range (age-adjusted and according to the normal reference range for the reporting laboratory); AND
         - **(2)** Patient meets ONE of the following [(a) or (b)]:
           - **(a)** Patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens); OR
           - **(b)** Patient has recurrent infections; OR
       - **c)** Patient has an IgG subclass deficiency, selective antibody deficiency (SAD), or another confirmed primary immunodeficiency and meets the following [(1) and (2)]:
         - **(1)** Patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens); AND
         - **(2)** Patient has recurrent infections; AND
     - **ii.** The medication is prescribed by or in consultation with one of the following physician specialists: an allergist, immunologist, otolaryngologist (ear nose and throat [ENT] physician), pulmonologist, or an infectious diseases physician who treats patients with primary immune deficiencies.
   - **B)** Patient is Currently Receiving Immune Globulin. Approve if the patient has been diagnosed with a primary immunodeficiency and according to the prescriber is continuing to receive benefit from the product.
     Note: Example of receiving benefit with the product includes increased IgG levels or prevention and/or controlling of infections.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of SCIG is not recommended in the following situations:

175. Selective Immune Globulin A (IgA) Deficiency as the Sole Immunologic Abnormality. Evidence does not support use of immune globulin.[15,24] Selective IgA deficiency is defined as a serum IgA level less than 0.07 g/L, but normal serum IgG and IgM levels in a patient > 4 years of age in whom other causes of hypogammaglobulinemia have been excluded.[11] Selective IgA deficiency may co-exist in some patients with poor specific IgG antibody production, with or without IgG2 subclass deficiency.[10,11] Some of these patients with a concomitant specific antibody defect may benefit from therapy with SCIG.

176. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Immune Globulin – Cytogam Prior Authorization Policy
- Cytogam® (human cytomegalovirus immune globulin intravenous infusion – Saol Therapeutics)

REVIEW DATE: 12/14/2022

OVERVIEW

Cytogam, a human cytomegalovirus (CMV) immune globulin intravenous (IGIV), is indicated for the **prophylaxis of CMV disease** associated with transplantation of kidney, lung, liver, pancreas, and heart.[1]

Other Uses With Supportive Evidence

Maternal transmission of CMV to the fetus may occur at any time during gestation, leading to congenital CMV.[2] A study of 304 pregnant women with a primary CMV infection were offered CMV IGIV. In the therapy group, 157 women were treated with CMV IGIV low dose (100 mg/kg/infusion given once every month) or high dose (200 mg/kg/infusion given once every 2 weeks for up to 3 doses if needed). The trial demonstrated that 56% of patients without CMV IGIV vs. 30% of patients receiving CMV IGIV developed congenital CMV infection.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cytogam. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cytogam as well as the monitoring required for adverse events and long-term efficacy, approval requires Cytogam to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cytogam is recommended in those who meet one of the following criteria:

FDA-Approved Indication

135. Prophylaxis of Cytomegalovirus Associated with Solid Organ Transplant. Approve for 4 months if the medication is prescribed by or in consultation with a physician affiliated with a transplant center, hematologist, or an infectious disease physician.

Other Uses with Supportive Evidence

136. Cytomegalovirus Associated with Pregnancy. Approve for 6 months if the medication is prescribed by or in consultation with an infectious disease physician or an obstetrician-gynecologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cytogam is not recommended in the following situations:

177. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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636. Cytogam intravenous infusion [prescribing information]. Roswell, GA: Saol Therapeutics; October 2020.
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PRIOR AUTHORIZATION POLICY

POLICY: Immunologicals – Adbry Prior Authorization Policy
- Adbry® (tralokinumab-ldrm subcutaneous injection – Leo)

REVIEW DATE: 03/22/2023; selected revision 05/10/2023 and 12/20/2023

OVERVIEW

Adbry, an interleukin (IL)-13 antagonist, is indicated for the treatment of moderate to severe **atopic dermatitis** in patients ≥ 12 years of age whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.[1] Adbry may be used with or without topical corticosteroids.

Clinical Efficacy

Three pivotal Adbry studies enrolled adults (≥ 18 years of age) with moderate to severe chronic atopic dermatitis affecting ≥ 10% of their body surface area (BSA).[1-3] Patients also had a recent of an inadequate response to a sufficient course of topical therapy (e.g., topical corticosteroids and/or topical calcineurin inhibitors). Inadequate response was defined as a failure to either achieve or maintain remission or low disease activity following at least 28 days of topical corticosteroid treatment (medium potency or higher) or for the maximum duration recommended by the topical corticosteroid prescribing information, with or without a topical calcineurin inhibitor. Patients who had received systemic treatment for atopic dermatitis in the previous year were also considered to be non-responders to topical therapies and were eligible for study inclusion. At Week 16, Adbry was found to be more effective in achieving a clinical response compared with placebo. In the monotherapy trials, the majority of patients who achieved a clinical response to Adbry at Week 16 experienced sustained efficacy at Week 52. Similarly, the patients enrolled in the Adbry pivotal trial in adolescents (12 to 17 years of age) had moderate to severe atopic dermatitis affecting 10% BSA or more and a previous inadequate response to topical medication (e.g., topical corticosteroids and/or topical calcineurin inhibitors).[4] As was observed in trials in adults, significantly more patients achieved a clinical response at Week 16 and again, efficacy was sustained through Week 52.

Guidelines

Guidelines for the care and management of atopic dermatitis (with topical therapies in adults [2022], with phototherapy and systemic agents [2023]) have been updated to address Adbry.[5,6] The guidelines note that despite the availability of newer, systemic therapies (e.g., Adbry), topical agents remain the mainstay of treatment due to their proven track record and favorable safety profiles. Several topical agents are recommended, with topical corticosteroids commonly used first-line for mild to severe atopic dermatitis in all skin regions. If topical therapy and basic management (e.g., moisturizers, bathing modifications) have been optimized and the patient has not achieved adequate control, consider an alternative diagnosis or systemic therapy. In this setting, use of Adbry is recommended in patients with moderate to severe disease (strong recommendation)

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Adbry. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Adbry as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Adbry to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Adbry is recommended in those who meet the following criteria:

FDA-Approved Indication

1. Atopic Dermatitis. Approve for the duration noted if the patient meets one of the following (A or B):
- **11.** Initial Therapy. Approve for 4 months if the patient meets the following (i, ii, iii, and iv):
  - **i.** Patient is ≥ 12 years of age; AND
  - **ii.** Patient has atopic dermatitis involvement estimated to be ≥ 10% of the body surface area according to the prescriber; AND
  - **iii.** Patient meets ALL of the following (a, b, and c):
    - **(1)** Patient has tried at least one medium-, medium-high, high-, and/or super-high-potency prescription topical corticosteroid; AND
    - **(2)** This topical corticosteroid was applied daily for at least 28 consecutive days; AND
    - **(3)** Inadequate efficacy was demonstrated with this topical corticosteroid therapy, according to the prescriber; AND
  - **iv.** The medication is prescribed by or in consultation with an allergist, immunologist, or dermatologist.
- **12.** Patient is Currently Receiving Adbry. Approve for 1 year if the patient meets the following (i and ii):
  - **i.** Patient has already received at least 4 months of therapy with Adbry; AND
    Note: A patient who has received < 4 months of therapy or who is restarting therapy with Adbry should be considered under criterion 1A (Atopic Dermatitis, Initial Therapy).
  - **ii.** Patient has responded to therapy as determined by the prescriber.
    Note: Examples of a response to Adbry therapy are marked improvements in erythema, induration/papulation/edema, excoriations, and lichenification; reduced pruritus; decreased requirement for other topical or systemic therapies; reduced body surface area affected with atopic dermatitis; or other observed responses.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Adbry is not recommended in the following situations:

52. **Asthma.** Adbry is not indicated for the treatment of asthma.[1] Three Phase III studies evaluated tralokinumab for the treatment of adults and adolescent patients with severe, uncontrolled asthma.[7,8] In STRATOS 1 and STRATOS 2 (published) [n = 1,202], Adbry 300 mg administered subcutaneously once every 2 weeks did not significantly reduce the annualized asthma exacerbation rate compared with placebo.[7] TROPOS (published) [n = 140] included patients with severe, uncontrolled asthma that required maintenance oral corticosteroid treatment plus inhaled corticosteroids and inhaled long-acting $beta_2$-agonists.[8] Following 40 weeks of therapy, the percent reduction from baseline in the final daily average oral corticosteroid dose was not significantly different between Adbry and placebo.

53. **Concurrent use of Adbry with another Monoclonal Antibody Therapy.** The efficacy and safety of Adbry in combination with other monoclonal antibodies have not been established.
Note: Examples of monoclonal antibody therapies are Dupixent® (dupilumab subcutaneous [SC] injection), Cinqair® (reslizumab intravenous injection), Fasenra® (benralizumab SC injection), Nucala® (mepolizumab SC injection), Teszpire® (tezepelumab-ekko SC injection), or Xolair® (omalizumab SC injection).

54. **Concurrent Use of Adbry with Janus Kinase (JAK) Inhibitors (oral or topical).** Use of JAK inhibitors is not recommended in combination with other JAK inhibitors, biologic immunomodulators (e.g., Adbry), or with other immunosuppressants.[9-11]
Note: Examples of JAK inhibitors are Cibinqo® (abrocitinib tablets), Rinvoq® (upadacitinib tablets), and Opzelura™ (ruxolitinib cream).

55. **Idiopathic Pulmonary Fibrosis**. Adbry is not indicated for the treatment of idiopathic pulmonary fibrosis.[1] Intravenous tralokinumab has been studied for the treatment of idiopathic pulmonary fibrosis in a Phase II, randomized, placebo-controlled study (published) [n = 176].[12] However, this study was terminated early after an interim analysis showed lack of efficacy. Two doses of tralokinumab were studied and neither dose significantly improved the least-squares mean difference percent predicted forced vital capacity from baseline to Week 52.

56. **Ulcerative Colitis.** Adbry is not indicated for the treatment of ulcerative colitis.[1] One Phase IIa, randomized, double-blind, placebo-controlled study (published) [n = 111] evaluated tralokinumab for the treatment of patients with moderate to severe ulcerative colitis despite standard treatments.[13] Following 8 weeks of therapy, tralokinumab did not significantly improve clinical response rates compared with placebo.

57. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Immunologicals – Cinqair Prior Authorization Policy
- Cinqair® (reslizumab intravenous infusion – Teva Respiratory)

REVIEW DATE: 03/22/2023

OVERVIEW

Cinqair, an interleukin-5 antagonist monoclonal antibody, is indicated for **severe asthma** as add-on maintenance treatment of patients ≥ 18 years of age who have an eosinophilic phenotype.[1] Limitations of Use: Cinqair is not indicated for the treatment of other eosinophilic conditions or for the relief of acute bronchospasm/status asthmaticus.

Clinical Efficacy

The Cinqair pivotal studies included adult and adolescent patients with moderate to severe asthma who had baseline blood eosinophil levels ≥ 400 cells/microliter despite therapy.[2-4] In one study that did not require patients to have elevated eosinophils at baseline, clinical benefit in regard to forced expiratory volume in 1 second (FEV_1) was not statistically significant with Cinqair vs. placebo. However, a significant improvement was observed in a subgroup of patients with baseline eosinophil levels ≥ 400 cells/microliter.

Guidelines

The Global Initiative for Asthma Global Strategy for Asthma Management and Prevention (2022) proposes a step-wise approach to asthma treatment.[5] Cinqair is listed as an option for add-on therapy in patients ≥ 18 years of age with difficult-to-treat, severe eosinophilic asthma (i.e., asthma that cannot be managed by therapy with medium- to high-dose inhaled corticosteroid [ICS]/formoterol [as both maintenance and reliever therapy] or medium- to high-dose ICS/long-acting $beta_2$-agonist [LABA] combination therapy with an as needed short-acting $beta_2$-agonist reliever, with or without an additional controller). Higher blood eosinophil levels, more exacerbations in the previous year, adult-onset asthma, nasal polyposis, a maintenance corticosteroid requirement at baseline, and low lung function (i.e., FEV_1 < 65% of predicted) may predict a good asthma response to Cinqair.

According to the European Respiratory Society/American Thoracic Society guidelines (2014; updated in 2020), severe asthma is defined as asthma which requires treatment with a high-dose ICS in addition to a second controller medication (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or asthma which remains uncontrolled despite this therapy.[6,7] Uncontrolled asthma is defined as asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids or asthma that meets one of the following four criteria:

1) Poor symptom control: Asthma Control Questionnaire consistently ≥ 1.5 or Asthma Control Test < 20;
2) Frequent severe exacerbations: two or more bursts of systemic corticosteroids in the previous year;
3) Serious exacerbations: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year;
4) Airflow limitation: FEV_1 < 80% predicted after appropriate bronchodilator withholding.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cinqair. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cinqair as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Cinqair to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cinqair is recommended in those who meet the following criteria:

FDA-Approved Indication

52. Asthma. Approve Cinqair for the duration noted if the patient meets one of the following conditions (A or B):

13. Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv, and v):

i. Patient is ≥ 18 years of age; AND

ii. Patient has a blood eosinophil count ≥ 400 cells per microliter within the previous 4 weeks or within 4 weeks prior to treatment with Cinqair or another monoclonal antibody therapy that may lower blood eosinophil levels; AND

Note: Examples of monoclonal antibody therapies that may lower blood eosinophil levels include Cinqair, Adbry (tralokinumab-ldrm subcutaneous injection), Dupixent (dupilumab subcutaneous injection), Fasenra (benralizumab subcutaneous injection), Nucala (mepolizumab subcutaneous injection), Tezspire (tezepelumab-ekko subcutaneous injection), and Xolair (omalizumab subcutaneous injection).

iii. Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):

a) An inhaled corticosteroid; AND

b) At least one additional asthma controller or asthma maintenance medication; AND

Note: Examples of additional asthma controller or asthma maintenance medications are inhaled long-acting beta$_2$-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, and monoclonal antibody therapies (e.g., Cinqair, Dupixent, Fasenra, Nucala, Tezspire, Xolair). Use of a combination inhaler containing both an inhaled corticosteroid and additional asthma controller/maintenance medication(s) would fulfil the requirement for both criteria a and b.

iv. Patient has asthma that is uncontrolled or was uncontrolled at baseline as defined by ONE of the following (a, b, c, d, or e):

FF) Note: "Baseline" is defined as prior to receiving Cinqair or another monoclonal antibody therapy for asthma. Examples of monoclonal antibody therapies for asthma include Cinqair, Dupixent, Fasenra, Nucala, Tezspire, and Xolair.

a) Patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR

b) Patient experienced one or more asthma exacerbation(s) requiring a hospitalization, an emergency department visit, or an urgent care visit in the previous year; OR

c) Patient has a forced expiratory volume in 1 second (FEV_1) < 80% predicted; OR

d) Patient has an FEV_1/forced vital capacity (FVC) < 0.80; OR

e) Patient has asthma that worsens upon tapering of oral (systemic) corticosteroid therapy; AND

v. The medication is prescribed by or in consultation with an allergist, immunologist, or pulmonologist.

14. Patient is Currently Receiving Cinqair. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):

i. Patient has already received at least 6 months of therapy with Cinqair; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with Cinqair should be considered under criterion 1A (Asthma, Initial Therapy).

ii. Patient continues to receive therapy with one inhaled corticosteroid or one inhaled corticosteroid-containing combination; AND

iii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Cinqair therapy are decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations, emergency department, urgent care, or medical clinic visits due to asthma; and decreased requirement for oral corticosteroid therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cinqair is not recommended in the following situations:

GG)

58. Concurrent use with another Monoclonal Antibody Therapy (i.e., Fasenra, Nucala, Dupixent, Tezspire, Xolair, or Adbry). The efficacy and safety of Cinqair used in combination with other monoclonal antibody therapies have not been established.

HH)

59. Eosinophilic Esophagitis or Eosinophilic Gastroenteritis. Cinqair is not indicated for the treatment of eosinophilic conditions other than asthma.[1] In addition to a small pilot study, one randomized, double-blind, placebo-controlled study (n =226) evaluated the efficacy of Cinqair in pediatric and adolescent patients with eosinophilic esophagitis.[8,9] In this study, patients were randomly assigned to receive Cinqair IV at varying doses for 12 weeks. At Week 15, peak esophageal eosinophil counts were reduced from baseline and all reductions with Cinqair were significant compared with placebo. Improvements in physician's global assessment scores were also observed in all groups (including placebo), but the difference between Cinqair and placebo was not statistically significant. Guidelines for the management of eosinophilic esophagitis from the American Gastroenterological Association and the Joint Task Force on Allergy-Immunology Practice Parameters (2020) only recommend using anti-interleukin-5 therapies in the context of a clinical trial.[10] Additional, well-controlled trials are needed to determine the role of Cinqair in the treatment of eosinophilic esophagitis and eosinophilic gastroenteritis.

60. Hypereosinophilic Syndrome. Cinqair is not indicated for the treatment of eosinophilic conditions other than asthma.[1] One very small pilot study (n = 4) evaluated the safety and efficacy of Cinqair in patients with hypereosinophilic syndrome who were refractory to or intolerant of treatment with conventional therapy.[11] A single dose of Cinqair resulted in a response in two of four patients. In the two responders, blood eosinophil counts dropped to within the normal range within 48 hours of the Cinqair infusion and this was accompanied by an improvement in clinical signs and symptoms. The World Health Organization-defined eosinophilic disorders update on diagnosis, risk stratification, and management (2022) notes that Cinqair has not been evaluated extensively for the treatment of hypereosinophilic syndrome.[12] Corticosteroids remain first-line therapy for hypereosinophilic syndrome. Additional, well-controlled trials are needed to determine the role of Cinqair in the treatment of hypereosinophilic syndrome.

61. Nasal Polyps. Cinqair is not indicated for the treatment of nasal polyps.[1] One double-blind, placebo-controlled, randomized safety and pharmacokinetic study (n = 24) evaluated the use of Cinqair in patients with nasal polyps.[13] Patients received a single infusion of either Cinqair 3 mg/kg, Cinqair 1 mg/kg, or placebo. It was reported that blood eosinophil counts and concentrations of eosinophil cation protein were reduced for up to 8 weeks following the Cinqair infusion. Nasal polyp scores improved for approximately 4 weeks in one-half of patients receiving active treatment. Additionally, a pooled subgroup analysis from the two pivotal Cinqair asthma exacerbation trials found that in patients with inadequately controlled asthma and chronic sinusitis with nasal polyps (n = 150) Cinqair demonstrated enhanced efficacy. Patients in this subgroup experienced an 83% reduction the clinical asthma exacerbation rate with Cinqair vs. placebo.[14] The magnitude of this reduction was greater than that observed with the overall study population. A Practice Parameter on the Diagnosis and Management of Rhinosinusitis (2014) and a Practice Parameter for the Management of Rhinitis (2020) from the Joint Task Force on Allergy-Immunology Practice Parameters, note that Cinqair has shown benefit in the treatment of patients with chronic rhinosinusitis with nasal polyps.[15-17] However, it is noted that Cinqair is not approved for this use. A Clinical Practice Guideline update on Adult Sinusitis from the American Academy of Otolaryngology (2015) address the management of nasal polyps, but do not address Cinqair.[18] Additional, well-designed, controlled trials are needed to determine the role of Cinqair in the treatment of patients with nasal polyps who do not have asthma.

62. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Immunologicals – Dupixent Prior Authorization Policy
- Dupixent® (dupilumab subcutaneous injection – Regeneron/sanofi-aventis)

REVIEW DATE: 03/22/2023; selected revision 05/10/2023

OVERVIEW

Dupixent, an interleukin-4 receptor alpha antagonist, is indicated for the following uses:[1]

- **Asthma,** as an add-on maintenance treatment in patients ≥ 6 years of age with moderate-to-severe disease with an eosinophilic phenotype or with oral corticosteroid-dependent asthma.
  Limitation of Use: Dupixent is not indicated for the relief of acute bronchospasm or status asthmaticus.
- **Atopic dermatitis,** for the treatment of patients ≥ 6 months of age with moderate-to-severe disease not adequately controlled with topical prescription therapies or when those therapies are not advisable.
- **Chronic rhinosinusitis with nasal polyposis (CRSwNP)** [i.e., nasal polyps], as an add-on maintenance treatment in adults with inadequately controlled disease.
- **Eosinophilic esophagitis**, in patients ≥ 12 years of age who weigh ≥ 40 kg.
- **Prurigo nodularis**, in patients ≥ 18 years of age.

Clinical Efficacy

Timing of efficacy assessments varied by indication across the numerous pivotal studies in which Dupixent demonstrated benefit. In the asthma trials, efficacy with Dupixent was assessed as early as 24 weeks.[2-5] In atopic dermatitis, the majority of studies evaluated the efficacy of Dupixent at 16 weeks.[1,6-10] The pivotal studies involving patients with CRSwNP evaluated the primary efficacy endpoints following 24 weeks of treatment.[1,11-13] Patients continued treatment with intranasal corticosteroids throughout the studies.

In Dupixent's eosinophilic esophagitis pivotal study, patients were required to have disease confirmed by baseline endoscopic biopsies with a demonstration of eosinophilic infiltration on central reading (peak cell count ≥ 15 eosinophils per high-powered field) that was unresponsive to an 8 week course of treatment with a high-dose proton pump inhibitor.[14] In total, 74.1% of patients had also previously received swallowed topical corticosteroids to treat their eosinophilic esophagitis. Patients with other causes of eosinophilic esophagitis, such as hypereosinophilic syndrome and eosinophilic granulomatosis with polyangiitis, were excluded from the study. In the first portion of this study, efficacy, as measured by objective assessments (e.g., intraepithelial eosinophil count) and subjective assessments (e.g., dysphagia symptoms), was evaluated after 24 weeks (6 months) of Dupixent therapy.

Two pivotal studies, PRIME and PRIME2, evaluated Dupixent's efficacy in the treatment of prurigo nodularis.[15,16] To enroll, patients were required to have ≥ 20 identifiable nodular lesions in total on both legs, and/or both arms, and/or trunk and to have failed a 2-week trial of a topical corticosteroid. Patients with prurigo nodularis secondary to medications or a medical condition such as neuropathy or psychiatric disease were excluded from the studies. The primary endpoint was evaluated at Week 24 in PRIME and initially at Week 12 and again at Week 24 in PRIME2.

Guidelines

Asthma Guidelines

The Global Initiative for Asthma Global Strategy for Asthma Management and Prevention (2022) proposes a stepwise approach to asthma treatment.[17] The majority of patients can be managed with an inhaled corticosteroid (ICS) with or without a long-acting beta$_2$-agonist and/or an additional controller. Dupixent is listed as an option for add-on therapy in patients ≥ 6 years of age with severe eosinophilic/Type 2 asthma or for patients ≥ 12 years of age who require treatment with a maintenance oral corticosteroid. Higher blood eosinophil levels and higher fractional concentration of exhaled nitric oxide may predict a good asthma response to Dupixent.

According to the European Respiratory Society/American Thoracic Society guidelines (2014; updated in 2020), severe asthma is defined as asthma which requires treatment with a high-dose ICS in addition to a second controller medication (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or asthma which remains uncontrolled despite this therapy.[18,19] Uncontrolled asthma is defined as asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids or asthma that meets one of the following four criteria:

5) Poor symptom control: Asthma Control Questionnaire consistently ≥ 1.5 or Asthma Control Test < 20; OR
6) Frequent severe exacerbations: two or more bursts of systemic corticosteroids in the previous year; OR
7) Serious exacerbations: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year; OR
8) Airflow limitation: FEV_1 < 80% predicted after appropriate bronchodilator witholding.

Atopic Dermatitis Guidelines

Guidelines for the care and management of atopic dermatitis (with topical therapies in adults [2022], with phototherapy and systemic agents [2014]) do not address Dupixent.[10,21] However, the guidelines note that topical therapies remain the cornerstone of treatment for atopic dermatitis due to their efficacy and generally favorable safety profiles. If patients fail topical therapy, use of systemic therapy may be considered. European guidelines on atopic eczema (2022) have been updated to address Dupixent.[22] Candidates for systemic treatment (i.e., Dupixent) are patients with severe, highly symptomatic disease, patients who have failed topical therapy, or patients who are unable to participate in normal daily life activities with their non-systemic treatment regimen.

Eosinophilic Esophagitis Guidelines

Guidelines for the management of eosinophilic esophagitis from the American Gastroenterological Association and the Joint Task Force on Allergy-Immunology Practice Parameters (2020) have not been updated since the FDA approval of Dupixent for this indication.[23] In patients with symptomatic disease, use of a proton pump inhibitor is recommended over no treatment, as is treatment with topical corticosteroids. Guidelines recommend diet modifications, such as an elemental diet (amino-acid based formulas) or an elimination diet, over no treatment. However, it is noted that patients who put a higher value on avoiding the challenges of adherence to these diets and the prolonged process of dietary reintroduction may reasonably decline this treatment option.

Nasal Polyp Guidelines

A 2014 Practice Parameter on the Diagnosis and Management of Rhinosinusitis, a 2020 Practice Parameter for the Management of Rhinitis from the Joint Task Force for Practice Parameters (JTFPP), and a 2015 Clinical Practice Guideline update on Adult Sinusitis from the American Academy of Otolaryngology (AAO) make similar recommendations regarding the diagnosis and management of CRSwNP.[24-27] The presence of two or more signs and symptoms of chronic rhinosinusitis (e.g., rhinorrhea, postnasal drainage,

anosmia, nasal congestion, facial pain, headache, fever, cough, and purulent discharge) that persist for an extended period of time makes the diagnosis chronic rhinosinusitis likely. However, this requires confirmation of sinonasal inflammation, which can either be done via direct visualization or computed tomography (CT) scan. Nasal corticosteroids are recommended for the management of CRSwNP, as they decrease nasal polyp size, prevent regrowth of nasal polyps following surgical removal, and improve nasal symptoms. Short courses of oral corticosteroids are also recommended. Endoscopic surgical intervention may be considered as an adjunct to medical therapy in patients with chronic rhinosinusitis that is not responsive or is poorly responsive to medical therapy. Dupixent is listed as a treatment option in the JTFPP practice parameter, but with no specific recommendations for use. The AAO guidelines do not address Dupixent.

The European Forum for Research and Education in Allergy expert board on uncontrolled severe CRSwNP and biologics (2021) recommends that these agents, including Dupixent, only be used for severe uncontrolled CRSwNP when Type 2 inflammation is present.[28] Severe CRSwNP is defined as bilateral CRSwNP with a nasal polyp score ≥ 4 and persistent symptoms (e.g., loss of smell/taste, nasal obstruction, secretion or postnasal drip, facial pain or pressure) with the need for add-on treatment to supplement intranasal corticosteroids. Severe CRSwNP is considered to be uncontrolled if the patient has received continuous treatment with an intranasal corticosteroid and has needed at least one course of systemic corticosteroids in the previous 2 years (or has a medical contraindication or intolerance) and/or has a previous sinonasal surgery.

Prurigo Nodularis Guidelines

A United States Expert Panel Consensus provides a practical approach for the diagnosis and management of prurigo nodularis (2021).[29] The primary findings in patients with prurigo nodularis are the presence of firm, nodular lesions; pruritus lasting at least 6 weeks; and or signs, or both, of repeated scratching, picking, or rubbing. Goals of treatment are to reduce pruritus, interrupt the itch-scratch cycle, and completely heal prurigo nodularis lesions.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Dupixent. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Dupixent as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Dupixent to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Dupixent is recommended in those who meet one of the following criteria:

FDA-Approved Indications

2. Asthma. Approve for the duration noted if the patient meets one of the following conditions (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv, and v):

i. Patient is ≥ 6 years of age; AND

ii. Patient meets ONE of the following criteria (a or b):

a) Patient has a blood eosinophil level ≥ 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to treatment with Dupixent or another monoclonal antibody therapy that may lower blood eosinophil levels; OR

Note: Examples of monoclonal antibody therapies that may lower blood eosinophil levels include Dupixent, Adbry (tralokinumab-ldrm subcutaneous injection), Cinqair (reslizumab intravenous infusion), Fasenra (benralizumab subcutaneous injection), Nucala (mepolizumab subcutaneous injection), Tezspire (tezepelumab subcutaneous injection), and Xolair (omalizumab subcutaneous injection).

b) Patient has oral (systemic) corticosteroid-dependent asthma according to the prescriber (e.g., the patient has received ≥ 5 mg oral prednisone or equivalent per day for ≥ 6 months); AND

iii. Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):

a) An inhaled corticosteroid; AND

b) At least one additional asthma controller or asthma maintenance medication; AND

Note: Examples of additional asthma controller or asthma maintenance medications are inhaled long-acting beta$_2$-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, and monoclonal antibody therapies for asthma (e.g., Cinqair, Fasenra, Nucala, Tezspire, and Xolair). Use of a combination inhaler containing both an inhaled corticosteroid and additional asthma controller/maintenance medication(s) would fulfil the requirement for both criteria a and b.

iv. Patient has asthma that is uncontrolled or was uncontrolled at baseline as defined by ONE of the following (a, b, c, d, or e):

Note: "Baseline" is defined as prior to receiving Dupixent or another monoclonal antibody therapy for asthma. Examples of monoclonal antibody therapies for asthma include Dupixent, Cinqair, Fasenra, Nucala, Tezspire, and Xolair.

a) Patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR

b) Patient experienced one or more asthma exacerbation(s) requiring a hospitalization, an emergency department visit, or an urgent care visit in the previous year; OR

c) Patient has a forced expiratory volume in 1 second (FEV_1) < 80% predicted; OR

d) Patient has an FEV_1/forced vital capacity (FVC) < 0.80; OR

e) Patient has asthma that worsens upon tapering of oral (systemic) corticosteroid therapy; AND

v. The medication is prescribed by or in consultation with an allergist, immunologist, or pulmonologist.

B) Patient is Currently Receiving Dupixent. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):

i. Patient has already received at least 6 months of therapy with Dupixent; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with Dupixent should be considered under criterion 1A (Asthma, Initial Therapy).

ii. Patient continues to receive therapy with one inhaled corticosteroid or one inhaled corticosteroid-containing combination inhaler; AND

iii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Dupixent therapy are decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations, emergency department visits, or urgent care visits due to asthma; decreased requirement for oral corticosteroid therapy.

3. Atopic Dermatitis. Approve for the duration noted if the patient meets one of the following conditions (A or B):

15. Initial Therapy. Approve for 4 months if the patient meets the following criteria (i, ii, iii, and iv):

i. Patient is ≥ 6 months of age; AND

ii. Patient has atopic dermatitis involvement estimated to be ≥ 10% of the body surface area according to the prescriber; AND

iii. Patient meets ALL of the following criteria (a, b, and c):

(1) Patient has tried at least one medium-, medium-high, high-, and/or super-high-potency prescription topical corticosteroid; AND

(2) This topical corticosteroid was applied daily for at least 28 consecutive days; AND

(3) Inadequate efficacy was demonstrated with this topical corticosteroid therapy, according to the prescriber; AND

iv. The medication is prescribed by or in consultation with an allergist, immunologist, or dermatologist.

16. Patient is Currently Receiving Dupixent. Approve for 1 year if the patient meets the following criteria (i and ii):

i. Patient has already received at least 4 months of therapy with Dupixent; AND
Note: A patient who has received < 4 months of therapy or who is restarting therapy with Dupixent should be considered under criterion 2A (Atopic Dermatitis, Initial Therapy).

ii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Dupixent therapy are marked improvements in erythema, induration/papulation/edema, excoriations, and lichenification; reduced pruritus; decreased requirement for other topical or systemic therapies; reduced body surface area affected with atopic dermatitis; or other responses observed.

4. Eosinophilic Esophagitis. Approve for the duration noted if the patient meets one of the following conditions (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv, v, vi and vii):

i. Patient is ≥ 12 years of age; AND

ii. Patient weighs ≥ 40 kg; AND

iii. Patient has a diagnosis of eosinophilic esophagitis as confirmed by an endoscopic biopsy demonstrating ≥ 15 intraepithelial eosinophils per high-power field; AND

iv. Patient does not have a secondary cause of eosinophilic esophagitis; AND
Note: Examples of secondary causes of eosinophilic esophagitis are hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis, and food allergy.

v. Patient has received at least 8 weeks of therapy with a proton pump inhibitor; AND

vi. Patient meets ONE of the following (a or b):

a) Patient has tried dietary modifications to treat/manage eosinophilic esophagitis; OR

b) The provider has determined that the patient is not an appropriate candidate for dietary modifications; AND
Note: Examples of dietary modifications to treat eosinophilic esophagitis include an elemental diet or an elimination diet.

vii. The medication is prescribed by or in consultation with an allergist or gastroenterologist.

B) Patient is Currently Receiving Dupixent. Approve for 1 year if the patient meets the following criteria (i and ii):

i. Patient has already received at least 6 months of therapy with Dupixent; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with Dupixent should be considered under criterion 3A (Eosinophilic Esophagitis, Initial Therapy).

ii. Patient has experienced a beneficial clinical response, defined by ONE of the following (a, b, or c):

a) Reduced intraepithelial eosinophil count; OR

b) Decreased dysphagia/pain upon swallowing; OR

c) Reduced frequency/severity of food impaction.

5. Nasal Polyps. Approve for the duration noted if the patient meets one of the following conditions (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv, v, and vi):

i. Patient is ≥ 18 years of age; AND

ii. Patient has chronic rhinosinusitis with nasal polyposis as evidenced by direct examination, endoscopy, or sinus computed **tomography (**CT) scan; AND

iii. Patient has experienced two or more of the following symptoms for at least 6 months: nasal congestion, nasal obstruction, nasal discharge, and/or reduction/loss of smell; AND

iv. Patient meets BOTH of the following (a and b):

38. Patient has received at least 3 months of therapy with an intranasal corticosteroid; AND

39. Patient will continue to receive therapy with an intranasal corticosteroid concomitantly with Dupixent; AND

v. Patient meets ONE of the following (a, b, or c):

a) Patient has received at least one course of treatment with a systemic corticosteroid for 5 days or more within the previous 2 years; OR

b) Patient has a contraindication to systemic corticosteroid therapy; OR

c) Patient has had prior surgery for nasal polyps; AND

vi. The medication is prescribed by or in consultation with an allergist, immunologist, or an otolaryngologist (ear, nose, and throat [ENT] physician specialist).

B) Patient is Currently Receiving Dupixent. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):

i. Patient has already received at least 6 months of therapy with Dupixent; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with Dupixent should be considered under criterion 3A (Nasal Polyps, Initial Therapy).

ii. Patient continues to receive therapy with an intranasal corticosteroid; AND

iii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Dupixent therapy are reduced nasal polyp size, improved nasal congestion, reduced sinus opacification, decreased sinonasal symptoms, improved sense of smell.

6. **Prurigo Nodularis.** Approve for the duration noted if the patient meets one of the following conditions (A or B):
   A) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv, v, and vi):
      i. Patient is ≥ 18 years of age; AND
      ii. Patient has ≥ 20 identifiable nodular lesions in total on both arms, and/or both legs, and/or trunk; AND
      iii. Patient has experienced pruritus for ≥ 6 weeks; AND
      iv. Patient meets ONE of the following (a or b):
         a) Patient's prurigo nodularis is NOT medication-induced or secondary to a non-dermatologic condition such as neuropathy or a psychiatric disease; OR
         b) The patient has a secondary cause of prurigo nodularis that has been identified and adequately managed, according to the prescriber; AND
      v. Patient meets ALL of the following criteria (a, b, and c):
         a) Patient has tried at least one high- or super-high-potency prescription topical corticosteroid; AND
         b) This topical corticosteroid was applied daily for at least 14 consecutive days; AND
         c) Inadequate efficacy was demonstrated with this topical corticosteroid therapy, according to the prescriber; AND
      vi. The medication is prescribed by or in consultation with an allergist, immunologist, or dermatologist.
   B) Patient is Currently Receiving Dupixent. Approve for 1 year if the patient meets the following criteria (i and ii):
      i. Patient has already received at least 6 months of therapy with Dupixent; AND
      Note: A patient who has received < 6 months of therapy or who is restarting therapy with Dupixent should be considered under criterion 5A (Prurigo Nodularis, Initial Therapy).
      ii. Patient has experienced a beneficial clinical response, defined by ONE of the following (a, b, or c):
         a) Reduced nodular lesion count; OR
         b) Decreased pruritus; OR
         c) Reduced nodular lesion size.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Dupixent is not recommended in the following situations:

63. **Concurrent Use of Dupixent with another Monoclonal Antibody Therapy (i.e., Adbry, Cinqair, Fasenra, Nucala, Tezspire, or Xolair).** The efficacy and safety of Dupixent in combination with other monoclonal antibody therapies have not been established.

64. **Concurrent Use of Dupixent with Janus Kinase Inhibitors (JAKis) [oral or topical].** Use of JAKis, such as Cibinqo® (abrocitinib tablets), Rinvoq® (upadacitinib tablets), and Opzelura™ (ruxolitinib cream), is not recommended for use in combination with other JAKis, biologic immunomodulators (e.g., Dupixent), or with other immunosuppressants.[30-32]

65. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Immunologicals – Fasenra Prior Authorization Policy
- Fasenra® (benralizumab subcutaneous injection – AstraZeneca)

REVIEW DATE: 03/22/2023

OVERVIEW

Fasenra, an interleukin-5 receptor alpha (IL-5Rα)-directed cytolytic monoclonal antibody, is indicated for **severe asthma** as add-on maintenance treatment of patients ≥ 12 years of age who have an eosinophilic phenotype.[1] Limitations of Use: Fasenra is not indicated for the treatment of other eosinophilic conditions or for the relief of acute bronchospasm/status asthmaticus.

Clinical Efficacy

In two pivotal asthma studies, the addition of Fasenra to existing therapy significantly reduced annualized asthma exacerbation rates in patients with baseline blood eosinophil levels ≥ 300 cells/microliter.[2-4] The magnitude of the improvements observed with Fasenra in this patient population were larger than those observed in patients with lower baseline eosinophil levels (e.g., < 150 cells/microliter). Another pivotal study involved adults with severe asthma receiving high-dose inhaled corticosteroid (ICS)/long-acting beta2-agonist (LABA) and chronic oral corticosteroid therapy who had a baseline blood eosinophil level ≥ 150 cells/microliter.[4]

Guidelines

The Global Initiative for Asthma Global Strategy for Asthma Management and Prevention (2022) proposes a step-wise approach to asthma treatment.[5] Fasenra is listed as an option for add-on therapy in patients ≥ 12 years of age with difficult-to-treat, severe eosinophilic asthma (i.e., asthma that cannot be managed by therapy with medium- to high-dose ICS/formoterol [as both maintenance and reliever therapy] or medium- to high-dose ICS/LABA combination therapy with an as needed short-acting beta$_2$-agonist reliever, with or without an additional controller). Higher blood eosinophil levels, more exacerbations in the previous year, adult-onset asthma, nasal polyposis, maintenance corticosteroid requirements, and low lung function may predict a good asthma response to Fasenra.

According to the European Respiratory Society/American Thoracic Society guidelines (2014; updated in 2020), severe asthma is defined as asthma which requires treatment with a high-dose ICS in addition to a second controller medication (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or asthma which remains uncontrolled despite this therapy.[6,7] Uncontrolled asthma is defined as asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids or asthma that meets one of the following four criteria:

9) Poor symptom control: Asthma Control Questionnaire consistently ≥ 1.5 or Asthma Control Test < 20;
10) Frequent severe exacerbations: two or more bursts of systemic corticosteroids in the previous year;
11) Serious exacerbations: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year;
12) Airflow limitation: forced expiratory volume in 1 second (FEV_1) < 80% predicted after appropriate bronchodilator withholding.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Fasenra. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Fasenra as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Fasenra to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Fasenra is recommended in those who meet the following criteria:

FDA-Approved Indication

53. Asthma. Approve Fasenra for the duration noted if the patient meets one of the following conditions (A or B):

17. Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv, and v):

i. Patient is ≥ 12 years of age; AND

ii. Patient has a blood eosinophil level ≥ 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to treatment with Fasenra or another monoclonal antibody therapy that may lower blood eosinophil levels; AND
Note: Examples of monoclonal antibody therapies that may lower blood eosinophil levels include Fasenra, Adbry (tralokinumab-ldrm subcutaneous injection), Cinqair (reslizumab intravenous infusion), Dupixent (dupilumab subcutaneous injection), Nucala (mepolizumab subcutaneous injection), Tezspire (tezepelumab-ekko subcutaneous injection), and Xolair (omalizumab subcutaneous injection).

iii. Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):
a) An inhaled corticosteroid; AND
b) At least one additional asthma controller or asthma maintenance medication; AND
II) Note: Examples of additional asthma controller or asthma maintenance medications are inhaled long-acting beta$_2$-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, and monoclonal antibody therapies for asthma (e.g., Cinqair, Dupixent, Fasenra, Nucala, Tezspire, Xolair). Use of a combination inhaler containing both an inhaled corticosteroid and additional asthma controller/maintenance medication(s) would fulfil the requirement for both criteria a and b.

iv. Patient has asthma that is uncontrolled or was uncontrolled at baseline as defined by ONE of the following (a, b, c, d, or e):
JJ) Note: "Baseline" is defined as prior to receiving Fasenra or another monoclonal antibody therapy for asthma. Examples of monoclonal antibody therapies for asthma include Fasenra, Cinqair, Dupixent, Nucala, Tezspire, and Xolair.
a) Patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR
b) Patient experienced one or more asthma exacerbation(s) requiring a hospitalization, an emergency department visit, or an urgent care visit in the previous year; OR
c) Patient has a forced expiratory volume in 1 second (FEV_1) < 80% predicted; OR

d) Patient has an FEV_1/forced vital capacity (FVC) < 0.80; OR

e) Patient has asthma that worsens upon tapering of oral (systemic) corticosteroid therapy; AND

v. The medication is prescribed by or in consultation with an allergist, immunologist, or pulmonologist.

18. Patient is Currently Receiving Fasenra. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):

i. Patient has already received at least 6 months of therapy with Fasenra; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with Fasenra should be considered under criterion 1A (Asthma, Initial Therapy).

ii. Patient continues to receive therapy with one inhaled corticosteroid or one inhaled corticosteroid-containing combination inhaler; AND

iii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Fasenra therapy are decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations, emergency department, urgent care, or medical clinic visits due to asthma; and decreased requirement for oral corticosteroid therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Fasenra is not recommended in the following situations:

66. Chronic Obstructive Pulmonary Disease (COPD). Fasenra is not indicated for the treatment of COPD.[1] One double-blind, placebo-controlled, Phase IIa study (n = 101) evaluated the efficacy and safety of Fasenra in patients 40 to 80 years of age with eosinophilia and moderate to severe COPD.[8] The annualized rate of acute COPD exacerbations was not reduced with Fasenra compared with placebo. Lung function was also not significantly improved with Fasenra vs. placebo. Numerically greater (although non-significant) improvements in exacerbations and lung function were observed with Fasenra vs. placebo in patients with baseline blood eosinophil levels of 200 cells/microliter or more. Two double-blind, placebo-controlled, Phase III studies (GALATHEA and TERRANOVA) also evaluated Fasenra in patients with moderate to very severe COPD (n = 1,120 and n = 1,545 patients, respectively, with eosinophils $\geq$ 220 cells/mm^3).[9] Following, 56 weeks of therapy, the annualized COPD exacerbation rates were not statistically significantly reduced with Fasenra vs. placebo in either study. Current COPD guidelines from the Global Initiative for Chronic Lung Disease (2022) note the negative data with Fasenra and state that further studies are needed.[10]

67. Concurrent use of Fasenra with another Monoclonal Antibody Therapy (i.e., Cinqair, Nucala, Dupixent, Tezspire, Xolair, or Adbry). The efficacy and safety of Fasenra used in combination with other monoclonal antibody therapies have not been established.

68. Hypereosinophilic Syndrome. Fasenra is not indicated for the treatment of eosinophilic conditions other than asthma.[1] A small, randomized, double-blind, placebo-controlled, Phase II trial (n = 20) evaluated the efficacy of Fasenra in patients who had platelet-derived growth factor receptor alpha (PDGFRA)-negative hypereosinophilic syndrome with an absolute eosinophil count of 1,000 cells/mm^3.[11] At Week 12, 90% of patients receiving Fasenra (n = 9/10) vs. 30% of patients receiving placebo (n = 3/10) achieved a 50% or greater reduction in the absolute eosinophil count (P = 0.02). Following the randomized phase, all patients received open-label Fasenra 30 mg every 4 weeks. During this time, 74% of patients (n = 14/19) had sustained clinical and hematologic responses for 48 weeks. The World Health Organization-defined eosinophilic disorders update on diagnosis, risk stratification, and management (2022) notes that corticosteroids remain first-line therapy for the treatment of

hypereosinophilic syndrome.[12] Available data with Fasenra is discussed, but this therapy continues to be considered investigational.

69. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Immunologicals – Nucala Prior Authorization Policy
- Nucala® (mepolizumab subcutaneous injection – GlaxoSmithKline)

REVIEW DATE: 03/22/2023

OVERVIEW

Nucala, an interleukin (IL)-5 antagonist monoclonal antibody, is indicated for the following uses:[1]

- **Asthma**, as add-on maintenance treatment of patients ≥ 6 years of age with severe disease with an eosinophilic phenotype. Limitations of Use: Nucala is not indicated for the relief of acute bronchospasm or status asthmaticus.
- **Chronic rhinosinusitis with nasal polyposis** (CRSwNP), as an add-on maintenance treatment in patients ≥ 18 years of age with an inadequate response to nasal corticosteroids.
- **Eosinophilic granulomatosis with polyangiitis** (EGPA) [formerly known as Churg-Strauss Syndrome] in adult patients.
- **Hypereosinophilic syndrome** (HES) in patients ≥ 12 years of age who have had HES for ≥ 6 months without an identifiable non-hematologic secondary cause.

Clinical Efficacy

Asthma

In the pivotal asthma studies of Nucala, patients were generally required to have elevated eosinophils at baseline (e.g., peripheral blood eosinophil count ≥ 150 cells/microliter at screening or ≥ 300 cells/microliter at some time during the previous year). Across the studies, efficacy was assessed as early as 24 weeks.[1-4]

Eosinophilic Granulomatosis with Polyangiitis

One study evaluated the efficacy of Nucala in patients ≥ 18 years of age with relapsing or refractory EGPA who had received ≥ 4 weeks of a stable oral corticosteroid dose (i.e., prednisolone, prednisone).[5] Patients were also required to have a baseline relative eosinophil level of 10% or an absolute eosinophil level > 1,000 cells per microliter; however, the baseline mean absolute eosinophil level was approximately 175 cells per microliter across both treatment groups. While remission benefit of Nucala was demonstrated in the overall patient population, the magnitude of improvements observed with Nucala were larger in patients with baseline eosinophil levels ≥ 150 cells per microliter than in patients with lower baseline levels.

Hypereosinophilic Syndrome

One study evaluated the efficacy of Nucala in patients ≥ 12 years of age with hypereosinophilic syndrome for ≥ 6 months.[6] Patients with non-hematologic secondary hypereosinophilic syndrome and those with FIP1L1-PDGFRα kinase-positive hypereosinophilic syndrome were excluded. All patients had a baseline blood eosinophil count ≥ 1,000 cells per microliter. Additionally, all patients had been on stable therapy for their hypereosinophilic syndrome (e.g., oral corticosteroids, immunosuppressive agents, or cytotoxic therapy) for 4 weeks or more prior to randomization. Efficacy was assessed following 32 weeks of therapy.

Nasal Polyps

In one pivotal study involving adult patients with chronic rhinosinusitis with nasal polyposis, the primary efficacy endpoints were assessed at 52 weeks.[1,7] However, improvements in nasal polyp size and symptoms compared with placebo were observed much earlier on in the course of treatment (i.e., between 9 and 24 weeks).

Guidelines

Asthma Guidelines

The Global Initiative for Asthma Global Strategy for Asthma Management and Prevention (2022) proposes a step-wise approach to asthma treatment.[8] Nucala is listed as an option for add-on therapy in patients ≥ 6 years of age with difficult-to-treat, severe eosinophilic asthma (i.e., asthma that cannot be managed by therapy with medium- to high-dose inhaled corticosteroid [ICS]/formoterol [as both maintenance and reliever therapy] or medium- to high-dose ICS/long-acting $beta_2$-agonist [LABA] combination therapy with an as needed short-acting $beta_2$-agonist reliever, with or without an additional controller). Higher blood eosinophil levels, more exacerbations in the previous year, adult-onset asthma, nasal polyposis, maintenance corticosteroid requirements, and low lung function may predict a good asthma response to Nucala.

According to the European Respiratory Society/American Thoracic Society guidelines (2014; updated in 2020), severe asthma is defined as asthma which requires treatment with a high-dose ICS in addition to a second controller medication (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or asthma which remains uncontrolled despite this therapy.[9,10] Uncontrolled asthma is defined as asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids or asthma that meets one of the following four criteria:

13) Poor symptom control: Asthma Control Questionnaire consistently ≥ 1.5 or Asthma Control Test < 20;
14) Frequent severe exacerbations: two or more bursts of systemic corticosteroids in the previous year;
15) Serious exacerbations: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year;
16) Airflow limitation: forced expiratory volume in 1 second (FEV_1) < 80% predicted after appropriate bronchodilator withholding.

EGPA Guidelines

The American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis (2021) includes recommendations regarding the management of EGPA.[11] For patients with active, non-severe EGPA, combination therapy with Nucala and corticosteroids is recommended over other traditional treatments such as methotrexate, azathioprine, or mycophenolate mofetil in the setting of remission induction. Non-severe EGPA is defined as vasculitis in the absence of life- or organ-threatening manifestations. In general, the clinical profile includes rhinosinusitis, asthma, mild systemic symptoms, uncomplicated cutaneous disease, and mild inflammatory arthritis. Nucala, in combination with corticosteroids, is also a recommended therapy for patients who have relapsed and are experiencing non-severe disease manifestations (i.e., asthma and/or sinonasal disease) while receiving either low-dose corticosteroids alone, methotrexate, azathioprine, or mycophenolate mofetil. In this same setting, Nucala therapy is preferred over Xolair (off-label use), even in patients with high serum immunoglobulin E (IgE) levels. For patients with severe EGPA, cyclophosphamide or rituximab is preferred over Nucala for remission induction. Similarly, for remission induction, methotrexate, azathioprine, or mycophenolate mofetil are recommended over Nucala in patients with severe disease. Severe EGPA is defined as vasculitis with life- or organ-threatening manifestations, such as alveolar hemorrhage, glomerulonephritis, central nervous system vasculitis, mononeuritis multiplex, cardiac involvement, mesenteric ischemia, or limb/digit ischemia.

Hypereosinophilia Guidelines
The World Health Organization-defined eosinophilic disorders update on diagnosis, risk stratification, and management (2022) notes that corticosteroids remain first-line therapy for the treatment of HES.[12] Nucala, hydroxyurea, pegylated-interferon, imatinib, and hematopoietic stem cell transplantation are listed as second-line treatment options.

Nasal Polyps Guidelines
A Practice Parameter on the Diagnosis and Management of Rhinosinusitis (2014), a Practice Parameter for the Management of Rhinitis (2020) from the Joint Task Force on Practice Parameters (JTFPP), and a Clinical Practice Guideline update on Adult Sinusitis (2015) from the American Academy of Otolaryngology (AAO) make similar recommendations regarding the diagnosis and management of CRSwNP.[13-17] The presence of two or more signs and symptoms of chronic rhinosinusitis (CRS) [e.g., rhinorrhea, postnasal drainage, anosmia, nasal congestion, facial pain, headache, fever, cough, and purulent discharge] that persist for an extended period of time makes the diagnosis CRS likely. However, this requires confirmation of sinonasal inflammation, which can either be done via direct visualization or computed tomography scan. Nasal corticosteroids are recommended for the management of CRSwNP, as they decrease nasal polyp size, prevent regrowth of nasal polyps following surgical removal, and improve nasal symptoms. Short courses of oral corticosteroids are also recommended. Endoscopic surgical intervention may be considered as an adjunct to medical therapy in patients with chronic rhinosinusitis that is not responsive or is poorly responsive to medical therapy. In the JTFPP practice parameter, Nucala is noted to have demonstrated benefit for the treatment of CRSwNP, but specific recommendations were not made. The AAO guidelines do not address Nucala.

The European Forum for Research and Education in Allergy expert board on uncontrolled severe CRSwNP and biologics (2021) recommends these agents, including Nucala, only be used for severe uncontrolled CRSwNP when Type 2 inflammation is present.[18] Severe CRSwNP is defined as bilateral CRSwNP with a nasal polyp score (NPS) ≥ 4 and persistent symptoms (e.g., loss of smell/taste, nasal obstruction, secretion or postnasal drip, facial pain or pressure) with the need for add-on treatment to supplement intranasal corticosteroids. Severe CRSwNP is considered to be uncontrolled if the patient has received continuous treatment with an intranasal corticosteroid and has needed at least one course of systemic corticosteroids in the previous 2 years (or has a medical contraindication or intolerance) and/or has a previous sinonasal surgery.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Nucala. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nucala as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Nucala to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Nucala is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Asthma. Approve Nucala for the duration noted if the patient meets one of the following conditions (A or B):

19. Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv, and v):

i. Patient is ≥ 6 years of age; AND

ii. Patient has a blood eosinophil level ≥ 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to treatment with Nucala or another monoclonal antibody therapy that may lower blood eosinophil levels; AND

Note: Examples of monoclonal antibody therapies that may lower blood eosinophil levels include Nucala, Adbry (tralokinumab-ldrm subcutaneous injection), Cinqair (reslizumab intravenous infusion), Dupixent (dupilumab subcutaneous injection), Fasenra (benralizumab subcutaneous injection), Tezspire (tezepelumab-ekko subcutaneous injection), Xolair (omalizumab subcutaneous injection).

iii. Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):

a) An inhaled corticosteroid; AND

b) At least one additional asthma controller or asthma maintenance medication; AND

Note: Examples of additional asthma controller or asthma maintenance medications are inhaled long-acting beta$_2$-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, and monoclonal antibody therapies for asthma (e.g., Cinqair, Dupixent, Fasenra, Nucala, Tezspire, and Xolair). Use of a combination inhaler containing both an inhaled corticosteroid and additional asthma controller/maintenance medication(s) would fulfil the requirement for both criteria a and b.

iv. Patient has asthma that is uncontrolled or was uncontrolled at baseline as defined by ONE of the following (a, b, c, d, or e):

LL) Note: "Baseline" is defined as prior to receiving Nucala or another monoclonal antibody therapy for asthma. Examples of monoclonal antibody therapies for asthma include Nucala, Cinqair, Dupixent, Fasenra, Tezspire, and Xolair.

a) Patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR

b) Patient experienced one or more asthma exacerbation(s) requiring a hospitalization, an emergency department visit, or an urgent care visit in the previous year; OR

c) Patient has a forced expiratory volume in 1 second (FEV_1) < 80% predicted; OR

d) Patient has an FEV_1/forced vital capacity (FVC) < 0.80; OR

e) Patient has asthma that worsens upon tapering of oral (systemic) corticosteroid therapy; AND

v. The medication is prescribed by or in consultation with an allergist, immunologist, or pulmonologist.

20. Patient is Currently Receiving Nucala. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):

i. Patient has already received at least 6 months of therapy with Nucala; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with Nucala should be considered under criterion 1A (Asthma, Initial Therapy).

ii. Patient continues to receive therapy with one inhaled corticosteroid or one inhaled corticosteroid-containing combination inhaler; AND

iii. Patient has responded to therapy as determined by the prescriber.

Note: Examples of a response to Nucala therapy are decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations, emergency department, urgent care,

or medical clinic visits due to asthma; and decreased requirement for oral corticosteroid therapy.

2. **Eosinophilic Granulomatosis with Polyangiitis (EGPA) [formerly known as Churg-Strauss Syndrome].** Approve Nucala for the duration noted if the patient meets one of the following conditions (A or B):
   3. Initial Therapy. Approve for 6 months if the patient meets ALL of the following conditions (i, ii, iii, iv, and v):
      - **i.** Patient is ≥ 18 years of age; AND
      - **ii.** Patient has active, non-severe disease; AND
        Note: Non-severe disease is defined as vasculitis without life- or organ-threatening manifestations. Examples of symptoms in patients with non-severe disease include rhinosinusitis, asthma, mild systemic symptoms, uncomplicated cutaneous disease, mild inflammatory arthritis.
      - **iii.** Patient has/had a blood eosinophil level ≥ 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to treatment with any monoclonal antibody therapy that may lower blood eosinophil levels; AND
        Note: Examples of monoclonal antibody therapies that may lower blood eosinophil levels include Nucala, Adbry (tralokinumab-ldrm subcutaneous injection), Cinqair (reslizumab intravenous infusion), Dupixent (dupilumab subcutaneous injection), Fasenra (benralizumab subcutaneous injection), Tezspire (tezepelumab-ekko subcutaneous injection), and Xolair (omalizumab subcutaneous injection).
      - **iv.** Patient has tried therapy with a corticosteroid (e.g., prednisone) for a minimum of 4 weeks; AND
      - **v.** The medication is prescribed by or in consultation with an allergist, immunologist, pulmonologist, or rheumatologist.
   4. Patient is Currently Receiving Nucala. Approve for 1 year if the patient meets the following criteria (i and ii):
      - **i.** Patient has already received at least 6 months of therapy with Nucala; AND
        Note: A patient who has received < 6 months of therapy or who is restarting therapy with Nucala should be considered under criterion 2A (Eosinophilic Granulomatosis with Polyangiitis, Initial Therapy).
      - **ii.** Patient has responded to therapy as determined by the prescriber.
        Note: Examples of a response to Nucala therapy are reduced rate of relapse, corticosteroid dose reduction, and reduced eosinophil levels.

5. **Hypereosinophilic Syndrome.** Approve Nucala for the duration noted if the patient meets one of the following conditions (A or B):
   6. Initial Therapy. Approve for 8 months if the patient meets ALL of the following conditions (i, ii, iii, iv, v, vi, and vii):
      - **i.** Patient is ≥ 12 years of age; AND;
      - **ii.** Patient has had hypereosinophilic syndrome for ≥ 6 months; AND
      - **iii.** Patient has FIP1L1-PDGFRα-negative disease; AND
      - **iv.** Patient does NOT have an identifiable non-hematologic secondary cause of hypereosinophilic syndrome according to the prescriber; AND
        Note: Examples of secondary causes of hypereosinophilic syndrome include drug hypersensitivity, parasitic helminth infection, human immunodeficiency virus infection, non-hematologic malignancy.
      - **v.** Patient has/had a blood eosinophil level ≥ 1,000 cells per microliter prior to treatment with any monoclonal antibody therapy that may lower blood eosinophil levels; AND

Note: Examples of monoclonal antibody therapies that may lower blood eosinophil levels include Nucala, Adbry (tralokinumab-ldrm subcutaneous injection), Cinqair (reslizumab intravenous infusion), Dupixent (dupilumab subcutaneous injection), Fasenra (benralizumab subcutaneous injection), Tezspire (tezepelumab-ekko subcutaneous injection), and Xolair (omalizumab subcutaneous injection).

vi. Patient has tried at least one other treatment for hypereosinophilic syndrome for a minimum of 4 weeks; AND

MM) Note: Example of treatments for hypereosinophilic syndrome include systemic corticosteroids, hydroxyurea, cyclosporine, imatinib, or pegylated-interferon.

vii. Nucala is prescribed by or in consultation with an allergist, immunologist, pulmonologist, or rheumatologist.

7. Patient is Currently Receiving Nucala. Approve for 1 year if the patient meets the following criteria (i and ii):

i. Patient has already received at least 8 months of therapy with Nucala; AND
Note: A patient who has received < 8 months of therapy or who is restarting therapy with Nucala should be considered under criterion 3A (Hypereosinophilic Syndrome, Initial Therapy).

ii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Nucala therapy are decreased number of flares, improved fatigue, reduced corticosteroid requirements, and decreased eosinophil levels.

8. Nasal Polyps. Approve Nucala for the duration noted if the patient meets one of the following conditions (A or B):

9. Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv, v, and vi):

10. Patient is ≥ 18 years of age; AND

11. Patient has chronic rhinosinusitis with nasal polyposis as evidenced by direct examination, endoscopy, or sinus computed **tomography (**CT) scan; AND

12. Patient has experienced two or more of the following symptoms for at least 6 months: nasal congestion, nasal obstruction, nasal discharge, and/or reduction/loss of smell; AND

13. Patient meets BOTH of the following (a and b):

40. Patient has received at least 3 months of therapy with an intranasal corticosteroid; AND

41. Patient will continue to receive therapy with an intranasal corticosteroid concomitantly with Nucala; AND

14. Patient meets ONE of the following (a, b, or c):

15. Patient has received at least one course of treatment with a systemic corticosteroid for 5 days or more within the previous 2 years; OR

16. Patient has a contraindication to systemic corticosteroid therapy; OR

17. Patient has had prior surgery for nasal polyps; AND

18. Nucala is prescribed by or in consultation with an allergist, immunologist, or an otolaryngologist (ear, nose and throat [ENT] physician specialist).

19. Patient is Currently Receiving Nucala. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):

20. Patient has already received at least 6 months of therapy with Nucala; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with Nucala should be considered under criterion 4A [Nasal Polyps, Initial Therapy]).

21. Patient continues to receive therapy with an intranasal corticosteroid; AND

22. Patient has responded to therapy as determined by the prescriber.

Note: Examples of a response to Nucala therapy are reduced nasal polyp size, improved nasal congestion, reduced sinus opacification, decreased sino-nasal symptoms, improved sense of smell.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nucala is not recommended in the following situations:

70. **Atopic Dermatitis.** Nucala is not indicated for the treatment of atopic dermatitis.[1] In one small study, intravenous (IV) mepolizumab significantly reduced peripheral blood eosinophil counts in patients with moderate to severe atopic dermatitis.[19,20] However, mepolizumab IV therapy did not result in clinical success as assessed by Physician's Global Assessment of Improvement scores compared with placebo. Other clinical outcomes were also not significantly improved with mepolizumab IV. Another small study evaluated subcutaneous Nucala in patients with moderate to severe atopic dermatitis.[21] Following 16 weeks of therapy, Nucala did not demonstrate efficacy, with 11% (n = 2/11) of patients meeting the primary endpoint of treatment success with Nucala vs. 0 with placebo.

71. **Chronic Obstructive Pulmonary Disease (COPD).** Nucala is not indicated for the treatment of COPD.[1] Two Phase III studies, METREX (n = 836) and METREO (n = 675) evaluated Nucala in patients with COPD who had a history of moderate or severe exacerbations despite treatment with inhaled triple therapy (inhaled corticosteroid/long-acting muscarinic antagonist/long-acting beta$_2$-agonist).[22] METREX included patients regardless of eosinophil counts, but did include a subgroup of patients who were considered to have an eosinophilic phenotype (eosinophil count ≥ 150 cells/microliter) [n = 462]. METREO only included patients with an eosinophilic phenotype (defined as an eosinophil count ≥ 150 cells/microliter at screening or ≥ 300 cells/microliter within the previous year). Overall, lower COPD exacerbation rates were observed with Nucala vs. placebo; however, none of these reductions were statistically significant in either the METREX overall modified intent to treat (mITT) population or the METREO mITT population (which included all eosinophilic phenotype patients). In the subgroup of patients in the METREX study with an eosinophilic phenotype, the COPD exacerbation rates were statistically lower with Nucala vs. placebo, as was the difference in the time to first exacerbation. In July 2018, the FDA's Pulmonary Allergy Drugs Advisory Committee voted against approval of Nucala as an add-on treatment to inhaled corticosteroid-based maintenance treatments to reduce flare-ups in patients with COPD.[23] The Committee had concerns about the defining criteria for the eosinophilic phenotype of COPD as well as the lack of data on patient asthma . Subsequently, in September 2018, the FDA rejected the approval of Nucala for COPD citing the need for additional clinical data. Current COPD guidelines from the Global Initiative for Chronic Lung Disease (2023) note the mixed data with Nucala.[24] The guidelines state that further studies are needed to determine if Nucala may have a role in a highly selected subgroup of patients with eosinophilic COPD.

72. **Concurrent use with another Monoclonal Antibody Therapy. (i.e., Cinqair, Fasenra, Dupixent, Tezspire, Xolair, or Adbry).** The efficacy and safety of Nucala used in combination with other monoclonal antibody therapies have not been established. A small number of case reports detailing combination use of Nucala and Xolair are available for both FDA-approved and off-label uses.[14,25-28] Further investigation is warranted.

73. Eosinophilic Esophagitis, Eosinophilic Gastroenteritis, or Eosinophilic Colitis. Nucala is not indicated for the treatment of eosinophilic esophagitis, eosinophilic gastroenteritis or eosinophilic colitis.[1] A few small studies have reported IV mepolizumab to be efficacious in these conditions.[29-31] Of note, Nucala is not approved for IV administration.[1] Guidelines for the management of eosinophilic esophagitis from the American Gastroenterological Association (AGA) and the Joint Task Force on Allergy-Immunology Practice Parameters (2020) only recommend using anti-interleukin-5 therapies in the context of a clinical trial.[32] Further research is warranted to determine if Nucala has a place in therapy in the treatment of these conditions.

74. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Immunologicals – Tezspire Prior Authorization Policy
- Tezspire® (tezepelumab-ekko subcutaneous injection – AstraZeneca/Amgen)

REVIEW DATE: 02/08/2023

OVERVIEW
Tezspire, a thymic stromal lymphopoietin (TSLP) blocker, is indicated as add-on maintenance treatment of patients ≥ 12 years of age with **severe asthma**.[1]
75.

Clinical Efficacy

Tezspire has been studied in patients ≥ 12 years of age with severe asthma.[2] The patients enrolled in the Phase III pivotal Tezspire trial had experienced two or more asthma exacerbations in the previous year, despite treatment with a medium- or high-dose inhaled corticosteroid (ICS) and one additional controller medication (e.g., long-acting beta$_2$-agonist [LABA], leukotriene antagonist).[2,3] In one study, 6 months of these previous therapies were required for enrollment, while in another, 12 months of ICS therapy with at least 3 months of additional controller therapy was required. In these trials, asthma exacerbation data was evaluated following 52 weeks of treatment. However, improvements in lung function parameters and symptom scores were reported as early as the first post-baseline assessment (i.e., 2 weeks of therapy).

Guidelines

The Global Initiative for Asthma Global Strategy for Asthma Management and Prevention (2022) proposes a step-wise approach to asthma treatment.[4] Tezspire is listed as an option for add-on therapy in patients ≥ 12 years of age with difficult-to-treat, severe asthma (i.e., asthma that cannot be managed by therapy with an ICS/LABA combination with or without an additional controller). Higher blood eosinophil levels and higher fractional exhaled nitric oxide may predict a good asthma response to Tezspire.

The European Respiratory Society/American Thoracic Society guidelines (2014; updated in 2020) define severe asthma as requiring treatment with a high-dose ICS in addition to a second controller medication (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or asthma which remains uncontrolled despite this therapy.[5,6] Uncontrolled asthma is defined as asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids or asthma that meets one of the following four criteria:

17) Poor symptom control: Asthma Control Questionnaire consistently ≥ 1.5 or Asthma Control Test < 20;
18) Frequent severe exacerbations: two or more bursts of systemic corticosteroids in the previous year;
19) Serious exacerbations: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year;

Airflow limitation: forced expiratory volume in 1 second (FEV_1) < 80% predicted after appropriate bronchodilator withholding.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Tezspire. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tezspire as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Tezspire to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Tezspire is recommended in those who meet the following criteria:

FDA-Approved Indication

23. Asthma. Approve Tezspire for the duration noted if the patient meets one of the following conditions (A or B):
21. Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, and iv):
i. Patient is ≥ 12 years of age; AND
ii. Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):
a) An inhaled corticosteroid; AND
b) At least one additional asthma controller or asthma maintenance medication; AND
76. Note: Examples of additional asthma controller or asthma maintenance medications are inhaled long-acting beta$_2$-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, and monoclonal antibody therapies for asthma (e.g., Tezspire, Cinqair [reslizumab intravenous infusion], Fasenra [benralizumab subcutaneous injection], Nucala [mepolizumab subcutaneous injection]), Dupixent (dupilumab subcutaneous injection), Xolair (omalizumab subcutaneous injection). Use of a combination inhaler containing both an inhaled corticosteroid and additional asthma controller/maintenance medication(s) would fulfill the requirement for both criteria a and b.
iii. Patient has asthma that is uncontrolled or was uncontrolled at baseline as defined by ONE of the following (a, b, c, d, or e):
77. Note: "Baseline" is defined as prior to receiving Tezspire or another monoclonal antibody therapy for asthma. Examples of monoclonal antibody therapies for asthma include Cinqair, Dupixent, Fasenra, Nucala, Tezspire, and Xolair.
a) Patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR
b) Patient experienced one or more asthma exacerbation(s) requiring a hospitalization, an emergency department visit, or an urgent care visit in the previous year; OR
c) Patient has a forced expiratory volume in 1 second (FEV_1) < 80% predicted; OR
d) Patient has an FEV_1/forced vital capacity (FVC) < 0.80; OR
e) Patient has asthma that worsens upon tapering of oral (systemic) corticosteroid therapy; AND
iv. The medication is prescribed by or in consultation with an allergist, immunologist, or pulmonologist.

22. Patient is Currently Receiving Tezspire. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):

i. Patient has already received at least 6 months of therapy with Tezspire; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with Tezspire should be considered under criterion 1A (Asthma, Initial Therapy).

ii. Patient continues to receive therapy with one inhaled corticosteroid or one inhaled corticosteroid-containing combination inhaler; AND

iii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Tezspire therapy are decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations, emergency department, urgent care, or medical clinic visits due to asthma; improved lung function parameters; and/or a decreased requirement for oral corticosteroid therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tezspire is not recommended in the following situations:

78. Atopic Dermatitis. Tezspire is not indicated for the treatment of atopic dermatitis.[1] One Phase IIa study, ALLEVIAD (published) [n = 113] evaluated the efficacy of Tezspire in combination with topical corticosteroids (TCS) vs. placebo in adults with moderate to severe atopic dermatitis.[7] At Week 12, a larger proportion of patients in the Tezspire + TCS group achieved a 50% reduction in the Eczema Area and Severity Index (primary efficacy endpoint) compared with placebo + TCS. However, this treatment difference was not statistically significant. Another Phase II, dose-ranging study in patients with atopic dermatitis was terminated prior to completion.[8]

79. Chronic Obstructive Pulmonary Disease (COPD). Tezspire is not indicated for the treatment of COPD.[1] One Phase II, randomized, double-blind, placebo-controlled trial, COURSE, is currently underway evaluating the efficacy of Tezspire in patients with moderate- to very severe-COPD who are continuing to experience exacerbations despite triple inhaled maintenance therapy (i.e., ICS/LABA/long-acting muscarinic antagonist).[8] Results are not yet available.

80.

81. Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP). Tezspire is not indicated for the treatment of CRSwNP.[1] One Phase III, randomized, double-blind, placebo-controlled trial, WAYPOINT, is currently underway evaluating the efficacy of Tezspire in adults with severe CRSwNP.[8] Results are not yet available.

82.

83. Chronic Spontaneous Urticaria. Tezspire is not indicated for the treatment of chronic spontaneous urticaria.[1] One Phase II, randomized, double-blind, placebo-controlled trial, INCEPTION, is currently underway evaluating the efficacy of Tezspire in patients with chronic spontaneous urticaria.[8] Results are not yet available.

84. Concurrent use of Tezspire with another Monoclonal Antibody Therapy (i.e., Cinqair, Fasenra, Nucala, Dupixent, Xolair, or Adbry). The efficacy and safety of Tezspire used in combination with other monoclonal antibody therapies have not been established.

85.

86. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Immunologicals – Xolair Prior Authorization Policy
- Xolair® (omalizumab subcutaneous injection – Genentech/Novartis)

REVIEW DATE: 03/22/2023

OVERVIEW

Xolair, an anti-immunoglobulin E (IgE) monoclonal antibody, is indicated for the following uses:[1]

- **Asthma,** in patients ≥ 6 years of age with moderate to severe persistent disease who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids (ICSs). Xolair has been shown to decrease the incidence of asthma exacerbations in these patients. Limitations of Use: Xolair is not indicated for the relief of acute bronchospasm or status asthmaticus. It is also not indicated for the treatment of other allergic conditions.
- **Chronic idiopathic urticaria**, in patients ≥ 12 years of age who remain symptomatic despite H1 antihistamine treatment. Limitation of Use: Xolair is not indicated for the treatment of other forms of urticaria.
- **Nasal polyps**, as add-on maintenance treatment in patients ≥ 18 years of age with an inadequate response to nasal corticosteroids.

Dosing of Xolair for the treatment of asthma or nasal polyps is based on body weight and the serum total IgE level measured before the start of treatment.[1] Dosing for these indications is only provided for patients with a pretreatment serum IgE level ≥ 30 IU/mL. Dosing of Xolair in patients with chronic idiopathic urticaria is not dependent on serum IgE level or body weight.

Clinical Efficacy

Timing of efficacy assessments varied by indication across the numerous pivotal studies in which Xolair demonstrated benefit. In the majority of the asthma trials, efficacy with Xolair was assessed as early as 16 weeks.[1-11] In chronic idiopathic urticaria, one of the studies included a 12-week double-blind treatment period, while the other was longer with 24 weeks of double-blind treatment.[12,13] Across both studies evaluating Xolair in nasal polyps, efficacy was evaluated at Week 24.[14] Patients continued treatment with intranasal corticosteroids throughout the study.

Guidelines

Asthma Guidelines

The Global Initiative for Asthma Global Strategy for Asthma Management and Prevention (2022) proposes a step-wise approach to asthma treatment.[15] Xolair is listed as an option for add-on therapy in patients ≥ 6 years of age with difficult-to-treat, severe eosinophilic asthma (i.e., asthma that cannot be managed by therapy with medium- to high-dose ICS/formoterol [as both maintenance and reliever therapy] or medium- to high-dose ICS/long-acting beta$_2$-agonist [LABA] combination therapy with an as needed short-acting beta$_2$-agonist reliever, with or without an additional controller). Higher blood eosinophil levels, elevated fractional exhaled nitric oxide, allergy-driven symptoms, and childhood-onset asthma may predict a good asthma response to Xolair.

According to the European Respiratory Society/American Thoracic Society guidelines (2014; updated in 2020), severe asthma is defined as asthma which requires treatment with a high-dose ICS in addition to a second controller medication (and/or systemic corticosteroids) to prevent it from becoming uncontrolled,

or asthma which remains uncontrolled despite this therapy.[16,17] Uncontrolled asthma is defined as asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids or asthma that meets one of the following four criteria:

20) Poor symptom control: Asthma Control Questionnaire consistently ≥ 1.5 or Asthma Control Test < 20;
21) Frequent severe exacerbations: two or more bursts of systemic corticosteroids in the previous year;
22) Serious exacerbations: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year;
23) Airflow limitation: forced expiratory volume in 1 second (FEV_1) < 80% predicted after appropriate bronchodilator withholding.

Chronic Urticaria Guidelines

A Practice Parameter on the Diagnosis and Management of Acute and Chronic Urticaria (2014) from the Joint Task Force on Practice Parameters (JTFPP) and guideline from the European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization (2018) define chronic urticaria as urticaria that has been continuously or intermittently present for at least 6 weeks.[18,19] Continuous therapy with antihistamines (second generation H1-antagonists) is generally recommended as first-line pharmacologic treatment for urticaria following trigger avoidance. If symptoms persist following 2 to 4 weeks of initial therapy, the dose of the second generation H1-antagonist should be increased to up to 4-fold. For patients with refractory chronic urticaria, the addition of Xolair may be considered.

Nasal Polyp Guidelines

A 2014 Practice Parameter on the Diagnosis and Management of Rhinosinusitis (2014) and a Practice Parameter for the Management of Rhinitis from the JTFPP (2020), and a 2015 Clinical Practice Guideline update on Adult Sinusitis from the American Academy of Otolaryngology (AAO), make similar recommendations regarding the diagnosis and management of chronic rhinosinusitis with nasal polyposis (CRSwNP).[20,22-24] The presence of two or more signs and symptoms of chronic rhinosinusitis (e.g., rhinorrhea, postnasal drainage, anosmia, nasal congestion, facial pain, headache, fever, cough, and purulent discharge) that persist for an extended period of time makes the diagnosis CRS likely. However, this requires confirmation of sinonasal inflammation, which can either be done via direct visualization or computed tomography scan. Nasal corticosteroids are recommended for the management of CRSwNP, as they decrease nasal polyp size, prevent regrowth of nasal polyps following surgical removal, and improve nasal symptoms. Short courses of oral corticosteroids are also recommended. Endoscopic surgical intervention may be considered as an adjunct to medical therapy in patients with chronic rhinosinusitis that is not responsive or is poorly responsive to medical therapy. The JTFPP parameter lists Xolair as a therapy that may be considered for the treatment of nasal polyps based on the limited data available at the time of publication. The AAO guidelines do not address Xolair.

The European Forum for Research and Education in Allergy expert board on uncontrolled severe CRSwNP and biologics (2021) recommends that these agents, including Xolair, only be used for severe uncontrolled CRSwNP when Type 2 inflammation is present.[49] Severe CRSwNP is defined as bilateral CRSwNP with a nasal polyp score ≥ 4 and persistent symptoms (e.g., loss of smell/taste, nasal obstruction, secretion or postnasal drip, facial pain or pressure) with the need for add-on treatment to supplement intranasal corticosteroids. Severe CRSwNP is considered to be uncontrolled if the patient has received continuous treatment with an intranasal corticosteroid and has needed at least one course of systemic corticosteroids in the previous 2 years (or has a medical contraindication or intolerance) and/or has a previous sinonasal surgery.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Xolair. All approvals are provided for the duration noted below. In cases where approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Xolair, as well as the monitoring required for adverse events and long-term efficacy, approval requires Xolair to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xolair is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Asthma.** Approve Xolair for the duration noted if the patient meets one of the following conditions (A or B):
   - **A)** Initial Therapy. Approve for 4 months if the patient meets the following criteria (i, ii, iii, iv, v, and vi):
     - **i.** Patient is ≥ 6 years of age; AND
     - **ii.** Patient has a baseline immunoglobulin E (IgE) level ≥ 30 IU/mL; AND
       Note: "Baseline" is defined as prior to receiving any treatment with Xolair or another monoclonal antibody therapy that may lower IgE levels (e.g., Dupixent [dupilumab subcutaneous injection], Tezspire [tezepelumab-ekko subcutaneous injection]).
     - **iii.** Patient has a baseline positive skin test or *in vitro* test (i.e., a blood test) for allergen-specific immunoglobulin E (IgE) for one or more perennial aeroallergens and/or for one or more seasonal aeroallergens; AND
       Note: "Baseline" is defined as prior to receiving any Xolair or another monoclonal antibody therapy that may interfere with allergen testing (e.g., Dupixent and Tezspire). Examples of perennial aeroallergens are house dust mite, animal dander, cockroach, feathers, and mold spores. Examples of seasonal aeroallergens are grass, pollen, and weeds.
     - **iv.** Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):
       - **a)** An inhaled corticosteroid; AND
       - **b)** At least one additional asthma controller or asthma maintenance medication; AND
         Note: Examples of additional asthma controller or asthma maintenance medications are inhaled long-acting beta$_2$-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, and monoclonal antibody therapies for asthma (e.g., Xolair, Cinqair (reslizumab intravenous infusion), Dupixent, Fasenra (benralizumab subcutaneous injection), Nucala (mepolizumab subcutaneous injection), and Tezspire. Use of a combination inhaler containing both an inhaled corticosteroid and additional asthma controller/maintenance medication(s) would fulfil the requirement for both criteria a and b.
     - **v.** Patient has asthma that is uncontrolled or was uncontrolled at baseline as defined by ONE of the following (a, b, c, d, or e):
       Note: "Baseline" is defined as prior to receiving Xolair or another monoclonal antibody therapy for asthma. Examples of monoclonal antibody therapies for asthma include Cinqair, Dupixent, Fasenra, Nucala, Tezspire, and Xolair.
       - **a)** Patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR

b) Patient experienced one or more asthma exacerbation(s) requiring a hospitalization, an emergency department visit, or an urgent care visit in the previous year; OR
c) Patient has a forced expiratory volume in 1 second (FEV_1) < 80% predicted; OR
d) Patient has an FEV_1/forced vital capacity (FVC) < 0.80; OR
e) Patient has asthma that worsens upon tapering of oral corticosteroid therapy; AND

vi. The medication is prescribed by or in consultation with an allergist, immunologist, or pulmonologist.

B) Patient is Currently Receiving Xolair. Approve Xolair for 1 year if the patient meets the following criteria (i, ii, and iii):

i. Patient has already received at least 4 months of therapy with Xolair; AND
Note: A patient who has received < 4 months of therapy or who is restarting therapy with Xolair should be considered under criterion 1A (Asthma, Initial Therapy).

ii. Patient continues to receive therapy with one inhaled corticosteroid or one inhaled corticosteroid-containing combination inhaler; AND

iii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Xolair therapy are decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations, emergency department, urgent care, or medical clinic visits due to asthma; decreased reliever/rescue medication use; and improved lung function parameters.

2. Chronic Idiopathic Urticaria (Chronic Spontaneous Urticaria). Approve Xolair for the duration noted if the patient meets one of the following conditions (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets the following criteria (i, ii, and iii):

i. Patient is ≥ 12 years of age; AND

ii. Patient has/had urticaria for > 6 weeks (prior to treatment with Xolair), with symptoms present > 3 days per week despite daily non-sedating H_1 antihistamine therapy with doses that have been titrated up to a maximum of four times the standard FDA-approved dose; AND
Note: Examples of non-sedating H_1 antihistamine therapy are cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine.

iii. The medication is prescribed by or in consultation with an allergist, immunologist, or dermatologist.

B) Patient is Currently Receiving Xolair. Approve Xolair for 1 year if the patient meets the following criteria (i and ii):

i. Patient has already received at least 4 months of therapy with Xolair; AND
Note: A patient who has received < 4 months of therapy or who is restarting therapy with Xolair should be considered under criterion 2A (Chronic Idiopathic Urticaria, Initial Therapy).

ii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Xolair therapy are decreased severity of itching, decreased number and/or size of hives.

3. Nasal Polyps. Approve Xolair for the duration noted if the patient meets one of the following conditions (A or B):

42. Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv, v, vi, and vii):

43. Patient is ≥ 18 years of age; AND

44. Patient has chronic rhinosinusitis with nasal polyposis as evidenced by direct examination, endoscopy, or sinus computed tomography (CT) scan; AND

45. Patient has experienced two or more of the following symptoms for at least 6 months: nasal congestion, nasal obstruction, nasal discharge, and/or reduction/loss of smell; AND

46. Patient has a baseline immunoglobulin E (IgE) level ≥ 30 IU/mL; AND

Note: "Baseline" is defined as prior to receiving any treatment with Xolair or another monoclonal antibody therapy that may lower IgE levels (e.g., Dupixent [dupilumab subcutaneous injection], Tezspire [tezepelumab-ekko subcutaneous injection]).

47. Patient meets BOTH of the following (a and b):
  48. Patient has received at least 3 months of therapy with an intranasal corticosteroid; AND
  49. Patient will continue to receive therapy with an intranasal corticosteroid concomitantly with Xolair; AND

50. Patient meets ONE of the following (a, b, or c):
  51. Patient has received at least one course of treatment with a systemic corticosteroid for 5 days or more within the previous 2 years; OR
  52. Patient has a contraindication to systemic corticosteroid therapy; OR
  53. Patient has had prior surgery for nasal polyps; AND

54. The medication is prescribed by or in consultation with an allergist, immunologist, or an otolaryngologist (ear, nose and throat [ENT] physician specialist).

55. Patient is currently receiving Xolair. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
  56. Patient has already received at least 6 months of therapy with Xolair; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy with Xolair should be considered under criterion 3A (Nasal Polyps, Initial Therapy).
  57. Patient continues to receive therapy with an intranasal corticosteroid; AND
  58. Patient has responded to Xolair therapy as determined by the prescriber.
  Note: Examples of a response to Xolair therapy are reduced nasal polyp size, improved nasal congestion, reduced sinus opacification, decreased sino-nasal symptoms, and/or improved sense of smell.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xolair is not recommended in the following situations:

1. **Atopic Dermatitis.** One single-center, double-blind, placebo-controlled trial, Atopic Dermatitis Anti-IgE Pediatric Trial (ADAPT) evaluated the efficacy of Xolair in patients 4 to 19 years of age with severe atopic dermatitis (n = 62).[25] After 24 weeks of therapy, the difference in the objective Scoring Atopic Dermatitis [SCORAD] index with Xolair vs. placebo was -6.9 (P = 0.01). This was statistically significant; however, the clinical significance is unknown. Quality of life measurements were also improved with Xolair. Smaller studies have not shown benefit and case studies have yielded mixed results.[25-27] Additional larger, well-designed clinical trials are needed to determine if Xolair has a role in the treatment of atopic dermatitis. Atopic dermatitis guidelines from the American Academy Dermatology (2014) note that data are limited to determine if Xolair is efficacious.[28] These guidelines do not make a recommendation regarding Xolair use in this patient population. European consensus guidelines for the treatment of atopic dermatitis (2018) also note the mixed data and state that they cannot recommend Xolair for the treatment of atopic dermatitis.[29]

2. **Concurrent use of Xolair with another Monoclonal Antibody Therapy (i.e., Cinqair, Fasenra, Dupixent, Nucala, Tezspire, or Adbry).** The efficacy and safety of Xolair used in combination with other monoclonal antibody therapies have not been established. There are very limited case reports describing the combined use of Nucala and Xolair for severe asthma as well as off-label indications.[21,30-32] Further investigation is warranted.
3. **Eosinophilic Gastroenteritis, Eosinophilic Esophagitis, or Eosinophilic Colitis.** There are limited and conflicting data from very small studies and case series on the use of Xolair for the treatment of eosinophilic gastrointestinal conditions.[33-36] Guidelines for the management of eosinophilic esophagitis

from the American Gastroenterological Association and the Joint Task Force on Allergy-Immunology Practice Parameters (2020) recommend against the use of Xolair in patients with this condition.[37]

4. **Latex Allergy in Health Care Workers with Occupational Latex Allergy.** A small European study assessed the effects of Xolair treatment in health care workers (n = 18) with occupational latex allergy.[38] Xolair use in these patients resulted in a reduction in mean conjunctival challenge test scores as compared with placebo-treated patients after 16-weeks of therapy. Also, three patients who did not respond to Xolair treatment during the double-blind phase responded during the 16-week open-label phase. Thus, the overall ocular response rate for all patients in the open-label phase was 93.8% (n = 15/16). Also 11 of 15 patients in the open-label phase had a negative response to a latex glove challenge test (4 patients had a mild response). Well-controlled trials are needed.

5. **Peanut and Other Food Allergies.** Limited data are available regarding the use of Xolair to facilitate desensitization to food allergens. A Phase II multicenter clinical trial was initiated using Xolair in patients with peanut allergy; however, it was discontinued prematurely due to concerns regarding the safety of the oral peanut challenges in some patients.[39] Insufficient data were obtained to reach any conclusions about the efficacy of Xolair. Data are also available from a Phase II study using Xolair as pretreatment in patients receiving multi-food oral immunotherapy, as well as a small pilot study examining the use of Xolair to facilitate rapid oral desensitization in high-risk peanut-allergic patients.[40,51] There are also minimal data (a Phase I study and a case series) on the use of Xolair to facilitate desensitization in patients with severe cow's milk allergy.[41-44] Additionally, a Phase I study and a Phase II study have evaluated the use of Xolair to facilitate desensitization in patients with multiple food allergies.[45,46] Guidelines for the diagnosis and management of food allergy in the US from the National Institute of Allergy and Infectious Diseases (2010; 2017 addendum) indicate there are currently no medications recommended to prevent IgE-mediated or non-IgE-mediated food-induced allergic reactions from occurring in an individual with existing food allergies.[47] The Practice Parameter on Food Allergy from the JTFPP (2014) also states that immunotherapies (such as the oral immunotherapy desensitization described above) show promise for the treatment of food allergy; however, there is currently inadequate evidence that the therapeutic benefit outweighs the risk.[48] Trials of these have been uncontrolled, small studies, which are subject to selection bias and uncertain safety profiles. However, treatment with anti-IgE monoclonal antibodies might increase the threshold for doses needed to stimulate an allergic reaction and potentially may enhance the safety profile for patients. A food allergy management guideline from the Global Allergy and Asthma European Network (2022) specifically states that no recommendation can be made for or against the use of Xolair for the treatment of food allergy due to insufficient evidence.[50] Additional well-controlled trials are needed.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Immunosuppressive Agents – Rezurock Prior Authorization Policy
- Rezurock™ (belumosudil tablets – Kadmon)

REVIEW DATE: 08/16/2023

OVERVIEW

Rezurock, a kinase inhibitor, is indicated for the treatment of patients ≥ 12 years of age with **chronic graft-versus-host disease** (GVHD) after failure of at least two prior lines of systemic therapy.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) Hematopoietic Cell Transplantation (version 1.2023 – March 31, 2023) guidelines recommend Rezurock for chronic GVHD as additional therapy in conjunction with systemic corticosteroids following failure (steroid-refractory disease) to ≥ two prior lines of systemic therapy.[2,3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Rezurock. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rezurock is recommended in those who meet the following criteria:

FDA-Approved Indication

137. Graft-Versus-Host Disease. Approve for 1 year if the patient meets the following (A, B, and C):
- **A)** Patient is ≥ 12 years of age; AND
- **B)** Patient has chronic graft-versus-host disease; AND
- **C)** Patient has tried at least two conventional systemic treatments for chronic graft-versus-host disease. Note: Examples of systemic therapy may include methylprednisolone, Imbruvica (ibrutinib capsules, tablets, or oral solution), cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil, imatinib.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rezurock is not recommended in the following situations:

178. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Infectious Disease – Impavido Prior Authorization Policy
- Impavido® (miltefosine capsules – Profounda)

REVIEW DATE: 04/19/2023

OVERVIEW

Impavido, an anti-leishmanial agent, is indicated in patients ≥ 12 years of age weighing ≥ 30 kg (66 lbs) for the treatment of:[1]

- **Visceral leishmaniasis** caused by *Leishmania donovani*.
- **Cutaneous leishmaniasis** caused by *L. braziliensis, L. guyanensis,* and *L. panamensis.*
- **Mucosal leishmaniasis** caused by *L. braziliensis.*

The treatment duration is 28 consecutive days. Limitation of use: *Leishmania* species studied in clinical trials evaluating Impavido were based on epidemiologic data; there may be geographic variation in clinical response of the same *Leishmania* species to Impavido; and the efficacy of Impavido in the treatment of other *Leishmania* species has not been evaluated.

A systematic review of four studies conducted in the Americas evaluated the efficacy of Impavido in pediatric patients ≤ 12 years of age with cutaneous leishmaniasis (n = 130).[2] The regimen was similar for all studies, with a target dose of 2.5 mg/kg/day (given as three times a day) for 28 days. The reported efficacy ranged from 63.1% to 82.8%.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Impavido. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Impavido as well as the monitoring required for adverse events and long-term efficacy, approval requires Impavido to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Impavido is recommended in those who meet the following criteria:

FDA-Approved Indication

36. Leishmaniasis. Approve for 1 month if the patient meets the following criteria (A and B):
- A) Patient meets one of the following (i, ii, or iii):
  - i. Patient has cutaneous leishmaniasis; OR
  - ii. Patient has mucosal leishmaniasis; OR
  - iii. Patient has visceral leishmaniasis; AND
- B) The medication was prescribed by or in consultation with an infectious diseases specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Impavido is not recommended in the following situations:

87. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Infectious Disease – Ivermectin Tablets Prior Authorization Policy
- Stromectol® (ivermectin tablets – Merck, generic)

REVIEW DATE: 09/13/2023

OVERVIEW

Ivermectin tablets (Stromectol, generic), an anthelmintic, are indicated for the treatment of intestinal (i.e., non-disseminated) **strongyloidiasis** due to the nematode parasite *Strongyloides stercoralis* and for the treatment of **onchocerciasis** due to the nematode parasite *Onchocerca volvulus*.[1] Ivermectin tablets do not have any activity against adult *O. volvulus* parasites and surgical excision of *O. volvulus* nodules is the recommended treatment.

The prescribing information notes that ivermectin tablets are given as a single oral dose for these two indications.[1] However, other sources note that ivermectin tablets should be given for 2 days for the treatment of strongyloidiasis.[1-3]

Off-Label Uses

Ivermectin has been used for many parasitic infections (off-label).[2,3,6] The Centers for Disease Control and Prevention (CDC) notes ivermectin tablets as a treatment option for the following: ascariasis, gnathostomiasis, hookworm-related cutaneous larva migrans, pediculosis (*pediculus humanus capitis*, *pediculus humanus corporis*, and pediculosis pubis [due to *Phthirus pubis*]), scabies, trichuriasis, and *Wucheria bancrofti* infection (a main cause of lymphatic filariasis).[7-15] There are data to support the use of ivermectin tablets for the treatment of enterobiasis, *Demodex folliculorum*, *Mansonella ozzardi* and *M. streptocerca* infections.[6,16]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of ivermectin tablets. All approvals are provided for 30 days, which is an adequate duration for the patient to receive the required number of doses.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of ivermectin tablets is recommended in those who meet one of the following criteria:

FDA-Approved Indications

59. Onchocerciasis Infection. Approve for one dose.

60. Strongyloidiasis. Approve for two doses.

Other Uses with Supportive Evidence

3. **Ascariasis.** Approve for one dose.

4. ***Demodex folliculorum* infection.** Approve for two doses.

•

5. **Enterobiasis (pinworm infection).** Approve for two doses.

6. **Gnathostomiasis.** Approve for one dose.

7. **Hookworm-related cutaneous larva migrans.** Approve for one dose.

8. ***Mansonella ozzardi* infection.** Approve for one dose.

9. ***Mansonella streptocerca* infection.** Approve for one dose.

10. **Pediculosis.** Approve for three doses if the patient meets one of the following (A, B, or C):
    - **A)** Patient has infection caused by *pediculus humanus capitis* (head lice); OR
    - **B)** Patient has infection caused by *pediculus humanus corporis* (body lice); OR
    - **C)** Patient has pediculosis pubis caused by *Phthirus pubis* (pubic lice).

11. **Scabies.** Approve for the duration noted below if the patient meets one of the following (A, B, C, D, or E):
    - **A)** Patient has classic scabies: Approve for two doses; OR
    - **B)** Patient has treatment-resistant scabies: Approve for two doses; OR
    - **C)** Patient is unable to tolerate topical treatment: Approve for two doses; OR
    - **D)** Patient has crusted scabies (i.e., Norwegian scabies): Approve for five doses; OR
    - **E)** Patient is using ivermectin tablets for prevention and/or control of scabies: Approve one dose.

12. **Trichuriasis.** Approve for three doses.

13. ***Wucheria bancrofti* infection.** Approve for one dose.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ivermectin tablets is not recommended in the following situations:

1. **Coronavirus disease 2019 (COVID-19).** The CDC's COVID-19 Treatment Guideline Panel reviewed studies that assessed the efficacy of oral ivermectin in the treatment of COVID-19.[17] The panel reviewed data from several clinical trials and cited the following findings: oral ivermectin did not reduce the need for emergency setting visits or hospitalizations when compared with placebo; there was no evidence of virologic or clinical benefit of using oral ivermectin; there was no evidence that oral ivermectin reduced progression to severe disease, improve time to resolution of symptoms; and compared with standard of care, oral ivermectin did not result in differences in all-cause mortality, hospital length of stay, or the need for mechanical ventilation. The Panel recommends **against** the use of ivermectin for the treatment of COVID-19, except in clinical trials.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Stromectol® tablets [prescribing information]. Whitehouse Station, NJ: Merck; May 2022.
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2023. Available at: https://www.clinicalkey.com/pharmacology/Accessed on September 5, 2023. Search term: ivermectin.
3. Facts and Comparisons® Online. Wolters Kluwer Health, Inc.; 2023. Available at: http://fco.factsandcomparisons.com/lco/action/homeAccessed on September 5, 2023. Search term: ivermectin.
4. Centers for Disease Control and Prevention. Parasites - Onchocerciasis (also known as river blindness). Available at: https://www.cdc.gov/parasites/onchocerciasis/. Accessed on September 5, 2023.
5. Centers for Disease Control and Prevention. Chapter 4. Travel-related infectious diseases. Available at: https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/strongyloidiasis. Accessed on September 5, 2023.
6. Micromedex® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/. Accessed on September 7, 2022. Search term: ivermectin.
7. Centers for Disease Control and Prevention. Parasites – Ascariasis. Available at: https://www.cdc.gov/parasites/ascariasis/index.html. Accessed on September 5, 2023.
8. Centers for Disease Control and Prevention. Parasites – Gnathostomiasis. Available at: https://www.cdc.gov/parasites/gnathostoma/health_professionals. Accessed on September 5, 2023.
9. Centers for Disease Control and Prevention. Parasites – Zoonotic Hookworm. Available at: https://www.cdc.gov/parasites/zoonotichookworm/health_professionals/index.html#tx. Accessed on September 5, 2023.
10. Centers for Disease Control and Prevention. Parasites – Head Lice. Available at: https://www.cdc.gov/parasites/lice/head/index.html. Accessed on September 5, 2023.
11. Centers for Disease Control and Prevention. Parasites – Body Lice. Available at: https://www.cdc.gov/parasites/lice/body/treatment.html. Accessed on September 5, 2023.
12. Centers for Disease Control and Prevention. Parasites – Pubic "Crab" Lice. Available at: https://www.cdc.gov/parasites/lice/pubic/index.html. Accessed on September 5, 2023.
13. Centers for Disease Control and Prevention. Parasites – Scabies. Available at: https://www.cdc.gov/parasites/scabies/index.html. Accessed on September 5, 2023.
14. Centers for Disease Control and Prevention. Parasites – Trichuriasis (also known as whipworm infection). Available at: https://www.cdc.gov/parasites/whipworm/health_professionals/index.html. Accessed on September 5, 2023.
15. Centers for Disease Control and Prevention. Parasites – Lymphatic filariasis. Available at: https://www.cdc.gov/parasites/lymphaticfilariasis/. Accessed on September 5, 2023.
16. Ta-Ting TH, Crainey JL, Post RJ, et al. Mansonellosis: current perspectives. *Res Rep Trop Med*. 2018;9:9-24.
17. Centers for Disease Control and Prevention – COVID-19 Treatment Guidelines – Ivermectin. Last updated April 29, 2022. Available at: https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ivermectin/. Accessed on September 5, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Infectious Disease – Livtencity Prior Authorization Policy
- Livtencity™ (maribavir tablets – Takeda)

REVIEW DATE: 12/06/2023

OVERVIEW

Livtencity, a protein kinase inhibitor, is indicated for the treatment of **post-transplant cytomegalovirus (CMV) infection/disease** that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir, or foscarnet in patients ≥ 12 years of age (weighing ≥ 35 kg).[1] Co-administration of Livtencity with ganciclovir or valganciclovir is not recommended; Livtencity may antagonize the antiviral activity of these agents. In the pivotal study (SOLSTICE), patients were treated with Livtencity (or another medication) for up to 8 weeks.

CMV infection is a common complication of hematopoietic-cell and solid-organ transplantation and is associated with increased morbidity and mortality.[2] The available antiviral agents (valganciclovir tablets or oral solution, ganciclovir injection, cidofovir injection, and foscarnet injection) are effective but use is limited by their toxic effects. In addition, approximately 5% to 14% of transplant recipients develop infection with drug-resistant CMV, which is associated with poor outcomes.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Livtencity. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Livtencity as well as the monitoring required for adverse events and long-term efficacy, approval requires Livtencity to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Livtencity is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Cytomegalovirus Infection – Treatment.** Approve for 2 months if the patient meets the following (A, B, C, D, E, and F):
   - **A)** Patient is ≥ 12 years of age; AND
   - **B)** Patient weighs ≥ 35 kg; AND
   - **C)** Patient is post-transplant; AND
     38. Note: This includes patients who are post- hematopoietic stem cell transplant or solid organ transplant.
   - **D)** Patient meets one of the following (i or ii):
     - **i.** Patient has cytomegalovirus infection/disease that is refractory to treatment with at least one of the following: cidofovir, foscarnet, ganciclovir, or valganciclovir; OR

ii. Patient has significant intolerance to ganciclovir or valganciclovir; AND

E) The medication is not prescribed in conjunction with ganciclovir or valganciclovir; AND

F) The medication is prescribed by or in consultation with a hematologist, infectious diseases specialist, oncologist, or a physician affiliated with a transplant center.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Livtencity is not recommended in the following situations:

88. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

275. Livtencity™ tablets [prescribing information]. Lexington, MA: Takeda; April 2023.
276. Maertens J, Cordonnier C, Jaksch P, et al. Maribavir for preemptive treatment of cytomegalovirus reactivation. *N Engl J Med*. 2019;381:1136-1147.

PRIOR AUTHORIZATION POLICY

POLICY: Infectious Disease – Pretomanid Prior Authorization Policy
- Pretomanid tablets (Global Alliance for TB Drug Development/Mylan)

REVIEW DATE: 12/06/2023

OVERVIEW

Pretomanid, a nitroimidazole, is indicated as part of a combination regimen with Sirturo® (bedaquiline tablets) and linezolid tablets or oral suspension (Zyvox®, generic) for the treatment of **pulmonary extensively drug-resistant or treatment-intolerant or nonresponsive multidrug-resistant tuberculosis (TB)** in adults.[1] Approval of this indication is based on limited clinical safety and efficacy data. This drug is indicated for use in a limited and specific population of patients.

Limitation of use: Pretomanid is not indicated for use in patients with the following conditions: drug-sensitive TB, latent infections due to *Mycobacterium tuberculosis*, extra-pulmonary infection due to *M. tuberculosis*, multidrug-resistant TB that is not treatment-intolerant or nonresponsive to standard therapy. The safety and effectiveness of Pretomanid when used with drugs other than Sirturo and linezolid have not been established.

The prescribing information notes the total duration of treatment with Pretomanid, Sirturo, and linezolid to be 26 weeks.[1] The dosing of the combination regimen can be extended beyond 26 weeks.[2]

Guidelines

The World Health Organization (WHO) issued a consolidated guidelines (2022) with information on the choice and design of regimens for the treatment of drug-resistant TB, including multidrug- or rifampin-resistant TB and confirmed rifampicin-susceptible, isoniazid-resistant TB.[2] Drug susceptibility tests are recommended to assist the prescriber in choosing the appropriate initial regimen. In addition, a surveillance system is recommended to determine the local prevalence of drug-resistant TB strains. The WHO notes that the duration of treatment is different for regimens containing different drugs. The duration for regimens containing Pretomanid, Sirturo, and linezolid range from 6 to 9 months.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Pretomanid. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Pretomanid as well as the monitoring required for adverse events and long-term efficacy, approval requires Pretomanid to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Pretomanid is recommended in those who meet the following criteria:

FDA-Approved Indication

61. Tuberculosis. Approve for 9 months if the patient meets the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets one of the following (i, ii, or iii):
  - **i.** Patient has extensively drug resistant tuberculosis; OR
  - **ii.** Patient has treatment-intolerant tuberculosis; OR
  - **iii.** Patient has nonresponsive multidrug-resistant tuberculosis; AND
- **C)** Pretomanid is prescribed in combination with Sirturo (bedaquiline tablets) and linezolid tablets or oral suspension (Zyvox, generic); AND
- **D)** The medication is prescribed by or in consultation with an infectious diseases specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Pretomanid is not recommended in the following situations:

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

277. Pretomanid tablets [prescribing information]. Limited Hyerabad, India: Mylan; December 2022.
278. World Health Organization consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022. Geneva: World Health Organization. 2022. Available at: https://www.who.int/publications/i/item/9789240063129. Accessed on December 1, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Infectious Disease – Pyrimethamine Prior Authorization Policy
- Daraprim® (pyrimethamine tablets – Vyera, generic)

REVIEW DATE: 12/06/2023

OVERVIEW

Pyrimethamine tablets (Daraprim, generic), a folic acid antagonist, are indicated for the treatment of **toxoplasmosis** when used conjointly with a sulfonamide, since synergism exists with this combination.[1]

Pyrimethamine tablets are considered to be the most effective drug against toxoplasmosis and are a standard component of therapy.[2] Leucovorin, a folinic acid, protects the bone marrow from the toxic effects of pyrimethamine and is prescribed in conjunction with pyrimethamine.

Guidelines

The Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with Human Immunodeficiency (HIV) [last updated September 2023] recommend pyrimethamine tablets as the drug of choice for treatment and chronic maintenance treatment (secondary prophylaxis) of *Toxoplasma gondii* encephalitis.[3] Pyrimethamine tablets are recommended as an option for: primary prophylaxis of *Toxoplasma gondii* encephalitis; primary prophylaxis and secondary prophylaxis (chronic maintenance treatment) of *Pneumocystis* pneumonia; and secondary prophylaxis (chronic maintenance treatment) and treatment of cystoisosporiasis (formerly isosporiasis). The drug of choice for these conditions is trimethoprim-sulfamethoxazole.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of pyrimethamine tablets. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with pyrimethamine tablets as well as the monitoring required for adverse events and long-term efficacy, approval requires pyrimethamine tablets to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of pyrimethamine tablets is recommended in those who meet one of the following criteria:

FDA-Approved Indication

20. Toxoplasmosis – Treatment. Approve for 1 year if the patient meets the following (A, B, and C):
- **a)** The medication is prescribed in combination with leucovorin; AND
- **b)** Patient meets one of the following (i or ii):
  - i. The medication is prescribed in combination with sulfadiazine; OR
  - ii. Patient meets both of the following (a and b):
    1. Patient is unable to take sulfadiazine; AND
    2. Patient meets one of the following (1 or 2):

a. The medication is prescribed in combination with systemic clindamycin; OR
b. The medication is prescribed in combination with atovaquone; AND

c) The medication is prescribed by or in consultation with an infectious diseases specialist or a physician specializing in the treatment of human immunodeficiency virus (HIV) infection.

Other Uses with Supportive Evidence

2. **Cystoisosporiasis (formerly known as isosporiasis) – Secondary Prophylaxis (Chronic Maintenance Treatment).** Approve for 1 year if the patient meets the following (A, B, and C):
   A) Patient has tried at least one other therapy for this condition; AND
   Note: Examples of other therapies used for this condition include trimethoprim-sulfamethoxazole and systemic ciprofloxacin.
   B) The medication is prescribed in combination with leucovorin; AND
   C) The medication is prescribed by or in consultation with an infectious diseases specialist or a physician specializing in the treatment of human immunodeficiency virus (HIV) infection.

3. **Cystoisosporiasis (formerly known as isosporiasis) – Treatment.** Approve for 1 year if the patient meets the following (A, B, and C):
   A) Patient has tried at least one other therapy for this condition; AND
   Note: Examples of other therapies used for this condition include trimethoprim-sulfamethoxazole and systemic ciprofloxacin.
   B) The medication is prescribed in combination with leucovorin; AND
   C) The medication is prescribed by or in consultation with an infectious diseases specialist or a physician specializing in the treatment of human immunodeficiency virus (HIV) infection.

4. ***Pneumocystis* Pneumonia – Primary Prophylaxis.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   A) Patient has tried at least one other therapy for this condition; AND
   Note: Examples of other therapies used for this condition include trimethoprim-sulfamethoxazole, systemic dapsone, aerosolized pentamidine (via Respigard II™ nebulizer), and atovaquone.
   B) The medication is prescribed in combination with leucovorin; AND
   C) Patient meets one of the following (i or ii):
   i. The medication is prescribed in combination with systemic dapsone; OR
   ii. The medication is prescribed in combination with atovaquone; AND
   D. The medication is prescribed by or in consultation with an infectious diseases specialist or a physician specializing in the treatment of human immunodeficiency virus (HIV) infection.

5. ***Pneumocystis* Pneumonia – Secondary Prophylaxis (Chronic Maintenance Therapy).** Approve for 1 year if the patient meets the following (A, B, C, and D):
   A) Patient has tried at least one other therapy for this condition; AND
   Note: Examples of other therapies used for this condition include trimethoprim-sulfamethoxazole, systemic dapsone, aerosolized pentamidine (via Respigard II™ nebulizer), and atovaquone.
   B) The medication is prescribed in combination with leucovorin; AND
   C) Patient meets one of the following (i or ii):
   i. The medication is prescribed in combination with systemic dapsone; OR
   ii. The medication is prescribed in combination with atovaquone; AND
   D) The medication is prescribed by or in consultation with an infectious diseases specialist or a physician specializing in the treatment of human immunodeficiency virus (HIV) infection.

6. ***Toxoplasma gondii* Encephalitis – Primary Prophylaxis.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   - **A)** Patient has tried at least one other therapy for this condition; AND
     Note: Examples of other therapies used for this condition include trimethoprim-sulfamethoxazole and atovaquone.
   - **B)** The medication is prescribed in combination with leucovorin; AND
   - **C)** Patient meets one of the following (i or ii):
     - **i.** The medication is prescribed in combination with systemic dapsone; OR
     - **ii.** The medication is prescribed in combination with atovaquone; AND
     - **D)** The medication is prescribed by or in consultation with an infectious diseases specialist or a physician specializing in the treatment of human immunodeficiency virus (HIV) infection.

7. ***Toxoplasma gondii* Encephalitis – Secondary Prophylaxis (Chronic Maintenance Therapy).** Approve for 1 year if the patient meets the following (A, B, and C):
   - **A)** The medication is prescribed in combination with leucovorin; AND
   - **B)** Patient meets one of the following (i or ii):
     - **i.** The medication is prescribed in combination with sulfadiazine; OR
     - **ii.** Patient meets both of the following (a and b):
       - **a)** Patient is unable to take sulfadiazine; AND
       - **b)** Patient meets one of the following (1 or 2):
         - **(1)** The medication is prescribed in combination with systemic clindamycin; OR
         - **(2)** The medication is prescribed in combination with atovaquone; AND
   - **C)** The medication is prescribed by or in consultation with an infectious diseases specialist or a physician specializing in the treatment of human immunodeficiency virus (HIV) infection.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of pyrimethamine is not recommended in the following situations:

8. **Malaria – Chemoprophylaxis or Treatment.** Pyrimethamine is no longer indicated for the treatment of acute malaria or for chemoprophylaxis of malaria.[1]

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

279. Daraprim® tablets [prescribing information]. New York, NY: Vyera; August 2017.
280. Centers for Disease Control and Prevention – Toxoplasmosis. Available at: https://www.cdc.gov/parasites/toxoplasmosis/index.html. Accessed on December 1, 2023.
281. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/whats-new-guidelines. Accessed on December 1, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Infectious Disease – Sirturo Prior Authorization Policy
- Sirturo® (bedaquiline fumarate tablets – Janssen)

REVIEW DATE: 12/06/2023

OVERVIEW

Sirturo, a diarylquinolone antimycobacterial, is indicated as part of a combination therapy in the treatment of **pulmonary multidrug-resistant tuberculosis (TB)** in patients ≥ 5 years of age (weighing ≥ 15 kg).[1] Reserve Sirturo for use when an effective treatment regimen cannot otherwise be provided. This indication is approved under accelerated approval based on time to sputum culture conversion. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Limitations of use: Sirturo should not be used for latent infections due to *Mycobacterium tuberculosis*, drug-sensitive TB, extra-pulmonary TB, and infections caused by non-tuberculous mycobacteria. The safety and efficacy of Sirturo in the treatment of patients infected with human immunodeficiency virus (HIV) with multidrug-resistant TB have not been established as clinical data are limited.

The prescribing information notes the total duration of treatment with Sirturo to be 24 weeks (adults and pediatric patients).[1]

Guidelines

The World Health Organization issued an operational handbook (2022) with information on the choice and design of regimens for the treatment of drug-resistant TB, including multidrug- or rifampin-resistant TB and confirmed rifampicin-susceptible, isoniazid-resistant TB.[2] Drug susceptibility tests are recommended to assist the prescriber in choosing the appropriate initial regimen. In addition, a surveillance system is recommended to determine the local prevalence of drug-resistant TB strains. There are different regimens that include Sirturo and other drugs (e.g., rifampicin, ethambutol, levofloxacin/moxifloxacin, pretomanid, linezolid, clofazimine). Sirturo is used for 6 to 9 months, whereas the other drugs in the regimen may be used for different duration.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Sirturo. All approvals are provided for the duration noted below. In cases where approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sirturo as well as the monitoring required for adverse events and long-term efficacy, approval requires Sirturo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sirturo is recommended in those who meet the following criteria:

FDA-Approved Indication

62. Tuberculosis. Approve for 9 months if the patient meets the following (A, B, C, D, and E):
- **E)** Patient is ≥ 5 years of age; AND
- **F)** Patient weighs ≥ 15 kg; AND
- **G)** Patient has multidrug-resistant tuberculosis; AND
- **H)** Sirturo is prescribed as part of a combination regimen with other anti-tuberculosis agents; AND
- **I)** The medication is prescribed by or in consultation with an infectious diseases specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sirturo is not recommended in the following situations:

10. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

282. Sirturo® tablets [prescribing information]. Titusville, NJ: Janssen; October 2023.
283. World Health Organization – Global Tuberculosis Report. 2022. Available at: https://iris.who.int/bitstream/handle/10665/363752/9789240061729-eng.pdf?sequence=1. Accessed on December 1, 2023.
284. World Health Organization consolidated guidelines on tuberculosis. Module 4: Treatment - drug-resistant tuberculosis treatment. Geneva: World Health Organization. 2022. Available at: https://iris.who.int/bitstream/handle/10665/365308/9789240063129-eng.pdf?sequence=1. Accessed on December 1, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Actemra Intravenous Prior Authorization Policy
- Actemra® (tocilizumab intravenous infusion – Genentech/Roche)

REVIEW DATE: 05/10/2023

OVERVIEW

Actemra intravenous infusion, an interleukin-6 (IL-6) receptor inhibitor, is indicated for the following conditions:[1]

- **Coronavirus Disease 2019 (COVID-19)**, in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).
- **Cytokine release syndrome**, in patients ≥ 2 years of age with severe or life-threatening disease associated with chimeric antigen receptor (CAR) T-cell therapy.
- **Giant cell arteritis** in adults.
- **Polyarticular juvenile idiopathic arthritis**, for the treatment of active disease in patients ≥ 2 years of age.
- **Rheumatoid arthritis**, for treatment of adults with moderate to severe active disease who have had an inadequate response to one or more disease modifying antirheumatic drugs (DMARDs).
- **Systemic juvenile idiopathic arthritis**, for the treatment of active disease in patients ≥ 2 years of age.

Guidelines/Clinical Efficacy

IL-6 blockers are mentioned in multiple guidelines for treatment of inflammatory conditions. Clinical data also support use of Actemra in other conditions.

- **Cytokine Release Syndrome:** The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for Management of Immunotherapy-Related Toxicities (version 1.2023 – March 10, 2023) give specific recommendations for use of Actemra in the management of inflammatory arthritis, cytokine release syndrome, and CAR T-cell-related toxicities.[6]
  - For cytokine release syndrome and CAR T-cell-related toxicities, Actemra is recommended for all grades of disease.
  - For immune checkpoint inhibitor-related inflammatory arthritis, infliximab and Actemra are among the alternatives that may be considered for severe arthritis not responding to steroids.
- **Giant Cell Arteritis and Polymyalgia Rheumatica:** Recommendations from the European League Against Rheumatism (EULAR) [2018] state the diagnosis of giant cell arteritis may be made without biopsy if there is a high suspicion of giant cell arteritis and a positive imaging test.[25] In the pivotal trial evaluating Actemra subcutaneous for giant cell arteritis (n = 251), patients were treated with corticosteroids in an open-label fashion (20 mg to 60 mg/day) during the screening period prior to treatment with Actemra subcutaneous.[31,32] Sustained remission at Week 52 was achieved in 56% of patients who received Actemra subcutaneous every week + 26-week prednisone taper and 53% of patients who received Actemra every other week + 26-week prednisone taper vs. in 14% of patients in the 26-week prednisone taper and 18% of patients in the 52-week prednisone taper.
- **Polyarticular Juvenile Idiopathic Arthritis:** Guidelines for the treatment of juvenile idiopathic arthritis from the American College of Rheumatology (ACR) [2021] address oligoarthritis and temporomandibular joint (TMJ) arthritis.[31] For oligoarthritis, a biologic is recommended following a trial of a conventional synthetic DMARD. In patients with TMJ arthritis, scheduled nonsteroidal

anti-inflammatory drugs (NSAIDs) and/or intra-articular glucocorticoids are recommended first-line. A biologic is a therapeutic option if there is an inadequate response or intolerance. Additionally, rapid escalation to a biologic ± conventional synthetic DMARD (methotrexate preferred) is often appropriate given the impact and destructive nature of TMJ arthritis. In these guidelines, there is not a preferred biologic that should be initiated for JIA. ACR/Arthritis Foundation has guidelines for the treatment of juvenile idiopathic arthritis (2019) specific to juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis.[7] For patients without risk factors, initial therapy with a DMARD is conditionally recommended over a biologic (including Actemra). Biologics (e.g., Actemra) are conditionally recommended as initial treatment when combined with a DMARD over biologic monotherapy.

- **Rheumatoid Arthritis:** Guidelines from ACR (2021) recommend addition of a biologic or a targeted synthetic DMARD for a patient taking the maximum tolerated dose of methotrexate who is not at target.[9]
- **Systemic Juvenile Idiopathic Arthritis:** Guidelines for the treatment of JIA from the ACR (2021) address systemic juvenile idiopathic arthritis (SJIA).[31] A brief trial of NSAIDs and/or an interleukin (IL)-1 or IL-6 inhibitor are recommended as initial monotherapy for patients with SJIA without macrophage activation syndrome. In a patient who presents with macrophage activation syndrome, an IL-1 or IL-6 blocker and/or systemic glucocorticoids are recommended.
- **Castleman's Disease:** The NCCN clinical practice guidelines for B-cell Lymphomas (version 2.2023 – February 8, 2023) mention Actemra as a second-line therapy for relapsed or refractory unicentric Castleman's disease in patients who are negative for the human immunodeficiency virus and human herpesvirus-8.[10] For multicentric Castleman's disease, the guidelines list Actemra as a subsequent therapy for relapsed, refractory, or progressive disease.
- **COVID-19 (Coronavirus Disease 2019):** By inhibiting IL-6, Actemra is speculated to be associated with better clinical outcomes in COVID-19, such as decreased systemic inflammation, improved survival rate, better hemodynamics, and improvement of respiratory distress.[24]
- **Stills Disease:** Still's disease presents in adults with features similar to those of SJIA.[11] Actemra IV has been effective in reducing fever, symptoms, and markers of inflammation in patients who were refractory to treatment with prednisone, methotrexate, Kineret, and/or a tumor necrosis factor inhibitor.[11-20]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Actemra intravenous. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of a patient treated with Actemra intravenous as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Actemra intravenous to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Actemra Intravenous is recommended in those who meet one of the following criteria:

FDA-Approved Indications

24. **COVID-19 (Coronavirus Disease 2019) – Hospitalized Patient.** For a patient who is hospitalized, forward all requests to the Medical Director. For a non-hospitalized patient, do not approve (refer to Conditions Not Recommended for Approval – COVID-19 – Non-Hospitalized Patient). Actemra intravenous is indicated for COVID-19 only in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[1] For COVID-19, the dose is 8 mg/kg (to a maximum of 800 mg) given as a single intravenous infusion. A second dose may be administered at least 8 hours after the initial infusion if clinical signs or symptoms worsen or do not improve after the first dose.
NN) Note: This includes requests for cytokine release syndrome in a patient hospitalized with COVID-19.

25. **Cytokine Release Syndrome Associated with Chimeric Antigen Receptor (CAR) T-Cell Therapy.** Approve for 1 week (which is adequate duration to receive four doses) if prescribed for a patient who has been or will be treated with a CAR T-cell therapy.
Note: Examples of CAR T-cell therapy include Abecma (idecabtagene vicleucel injection), Breyanzi (lisocabtagene maraleucel intravenous infusion), Kymriah (tisagenlecleucel intravenous infusion), Tecartus (brexucabtagene intravenous infusion), and Yescarta (axicabtagene ciloleucel intravenous infusion). If the patient has **Cytokine Release Syndrome due to COVID-19** (coronavirus disease 2019) refer to criteria for Other Uses With Supportive Evidence (below).

26. **Giant Cell Arteritis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
    27. Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):
        28. Patient has tried one systemic corticosteroid; AND
            Note: An example of a systemic corticosteroid is prednisone.
        29. The medication is prescribed by or in consultation with a rheumatologist.
    30. Patient is Currently Receiving Actemra (Subcutaneous or Intravenous). Approve for 1 year if the patient meets BOTH of the following (i and ii):
        i. Patient has been established on therapy for at least 6 months; AND
        OO) Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).
        ii. Patient meets at least ONE of the following (a or b):
            a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Actemra); OR
            PP) Note: Examples of objective measures are serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), resolution of fever, and/or reduced dosage of corticosteroids.
            QQ) b) Compared with baseline (prior to initiating Actemra), patient experienced an improvement in at least one symptom, such as decreased headache, scalp, or jaw pain; decreased fatigue; and/or improved vision.

31. **Polyarticular Juvenile Idiopathic Arthritis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
    A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):
        i. Patient meets one of the following conditions (a, b, c, or d):
            a) Patient has tried one other systemic therapy for this condition; OR
                i. Note: Examples of other systemic therapies include methotrexate, sulfasalazine, leflunomide, or a nonsteroidal anti-inflammatory drug (NSAID). A biologic (refer to

Appendix for examples of biologics used for polyarticular juvenile idiopathic arthritis) also counts as a trial of one systemic therapy.

b) Patient will be starting on Actemra intravenous concurrently with methotrexate, sulfasalazine, or leflunomide; OR

c) Patient has an absolute contraindication to methotrexate, sulfasalazine, or leflunomide; OR

ii. Note: Examples of absolute contraindication to methotrexate include pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, and blood dyscrasias.

d) Patient has aggressive disease, as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Actemra Intravenous or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Actemra); OR

Note: Examples of objective measures include Physician Global Assessment (MD global), Parent/Patient Global Assessment of Overall Well-Being (PGA), Parent/Patient Global Assessment of Disease Activity (PDA), Juvenile Arthritis Disease Activity Score (JDAS), Clinical Juvenile Arthritis Disease Activity Score (cJDAS), Juvenile Spondyloarthritis Disease Activity Index (JSpADA), serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating Actemra), patient experienced an improvement in at least one symptom, such as improvement in limitation of motion, less joint pain or tenderness, decreased duration of morning stiffness or fatigue, improved function or activities of daily living.

32. Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

33. Initial Therapy. Approve for 6 months if the patient meets both of the following (i and ii):

i. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND

Note: Examples of one conventional DMARD tried include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already had a 3-month trial of at least one biologic (refer to **Appendix** for examples of biologics used for rheumatoid arthritis). A patient who has already tried a biologic for rheumatoid arthritis is not required to "step back" and try a conventional synthetic DMARD.

ii. The medication is prescribed by or in consultation with a rheumatologist.

34. Patient is Currently Receiving Actemra Intravenous or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND

RR) Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least ONE of the following (a or b):

a) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR

Note: Examples of standardized and validated measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte

sedimentation rate (ESR) or C-reactive protein (CRP), Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).

b) Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

~~35.~~ Systemic Juvenile Idiopathic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i and ii):

i. The patient has tried one other systemic therapy for this condition; AND

Note: Examples of other systemic therapies include a corticosteroid (oral, intravenous), a conventional synthetic disease-modifying antirheumatic drug (DMARD) [e.g., methotrexate, leflunomide, sulfasalazine], or a 1-month trial of a nonsteroidal anti-inflammatory drug (NSAID). A previous trial of a biologic such as Kineret (anakinra subcutaneous injection), a tumor necrosis factor inhibitor (e.g., an etanercept product, an adalimumab product, or an infliximab product, or Ilaris [canakinumab subcutaneous injection]) also counts towards a trial of one other systemic agent for systemic juvenile idiopathic arthritis.

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Actemra Intravenous or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR

Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

Other Uses with Supportive Evidence

36. Castleman's Disease. Approve for the duration noted if the patient meets ONE of the following conditions (A or B):

37. Initial Approval. Approve for 6 months if the medication is prescribed by or in consultation with an oncologist or hematologist.

38. Patient is Currently Receiving Actemra Intravenous or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

39. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

40. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR

Note: Examples of objective measures include clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate, fibrinogen, albumin, and/or hemoglobin), increased body mass index, and/or reduction in lymphadenopathy.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as improvement or resolution of constitutional symptoms (e.g., fatigue, physical function).

41. Inflammatory Arthritis Associated with Checkpoint Inhibitor Therapy. Approve for the duration noted if the patient meets ONE of the following (A or B):

Note: Examples of checkpoint inhibitors are Keytruda (pembrolizumab intravenous infusion), Opdivo (nivolumab intravenous infusion), Yervoy (ipilimumab intravenous infusion), Tecentriq (atezolizumab intravenous infusion), Bavencio (avelumab intravenous infusion), Imfinzi (durvalumab intravenous infusion), and Libtayo (cemiplimab-rwlc intravenous infusion).

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient is symptomatic despite a trial of at least ONE systemic corticosteroid; AND
Note: Examples of a corticosteroid include methylprednisolone and prednisone.

ii. Patient has tried at least ONE systemic nonsteroidal anti-inflammatory agent (NSAID); AND
Note: Examples of systemic NSAIDs include ibuprofen and naproxen.

iii. The medication is prescribed by or in consultation with a rheumatologist or an oncologist.

B) Patient is Currently Receiving Actemra Intravenous or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
SS) Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate) and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

42. Polymyalgia Rheumatica. Approve for the duration noted if the patient meets ONE of the following (A or B):

43. Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

44. Patient has tried one systemic corticosteroid; AND
Note: An example of a systemic corticosteroid is prednisone.

45. The medication is prescribed by or in consultation with a rheumatologist.

46. Patient is Currently Receiving Actemra (Subcutaneous or Intravenous). Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
TT) Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Actemra); OR

UU) Note: Examples of objective measures are serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), resolution of fever, and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating Actemra), patient experienced an improvement in at least one symptom, such as decreased shoulder, neck, upper arm, hip, or thigh pain or stiffness; improved range of motion; and/or decreased fatigue.

10. Still's Disease. Approve for the duration noted if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient has tried one corticosteroid; AND

ii. Patient has tried one conventional synthetic disease-modifying antirheumatic drug (DMARD) such as methotrexate given for at least 2 months or was intolerant to a conventional synthetic DMARD; AND

iii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Actemra Intravenous or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on this medication for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Actemra Intravenous is not recommended in the following situations:

iii.

1. COVID-19 (Coronavirus Disease 2019) – Non-Hospitalized Patient. Actemra intravenous is only indicated in hospitalized adults with COVID who are receiving systemic corticosteroids and requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[1] For COVID-19, the dose is 8 mg/kg (to a maximum of 800 mg) given as a single intravenous infusion. A second dose may be administered at least 8 hours after the initial infusion if clinical signs or symptoms worsen or do not improve after the first dose.

2. Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD). Data are lacking evaluating concomitant use of Actemra intravenous in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see **Appendix** for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher rate of adverse effects and lack of controlled trial data in support of additive efficacy.[21-22]
Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Actemra intravenous.

3. **Crohn's Disease.** In a 12-week pilot study conducted in Japan, 36 adults with active Crohn's disease (Crohn's Disease Activity Index [CDAI] ≥ 150 and increased C-reactive protein) were randomized, in a double-blind fashion to Actemra 8 mg/kg intravenous every 2 weeks; or alternating infusions of Actemra 8 mg/kg every 4 weeks and placebo (i.e., alternating with placebo every 2 weeks), or to placebo every 2 weeks.[23] At baseline the CDAI means ranged from 287 to 306. Patients had been treated with corticosteroids, mesalamine-type drugs, metronidazole, or elemental diet. Six patients in the placebo group, four patients on Actemra intravenous every 4 weeks and one patient on Actemra intravenous every 2 weeks dropped out. The mean reduction in the CDAI score in the Actemra 8 mg/kg every 2 week group was 88 points (from mean 306 to 218). Further studies are needed.

iv.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARDs – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Actemra Subcutaneous Prior Authorization Policy
- Actemra® (tocilizumab subcutaneous injection – Genentech/Roche)

REVIEW DATE: 05/10/2023

OVERVIEW

Actemra subcutaneous injection, an interleukin-6 (IL-6) receptor inhibitor, is approved for the following uses:[1]

- **Giant cell arteritis** in adults.
- **Interstitial lung disease associated with systemic sclerosis,** to slow the rate of decline in pulmonary function in adults.
- **Polyarticular juvenile idiopathic arthritis**, for the treatment of active disease in patients ≥ 2 years of age.
- **Rheumatoid arthritis**, for treatment of adults with moderate to severe active disease who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs).
- **Systemic juvenile idiopathic arthritis**, for the treatment of active disease in patients ≥ 2 years of age.

Guidelines/Clinical Efficacy

IL-6 blockers are mentioned in multiple guidelines for treatment of inflammatory conditions. Clinical data also support use of Actemra in other conditions.

- **Giant Cell Arteritis and Polymyalgia Rheumatica:** Recommendations from the European League Against Rheumatism (EULAR) [2018] state the diagnosis of giant cell arteritis may be made without biopsy if there is a high suspicion of giant cell arteritis and a positive imaging test.[4] In the pivotal trial evaluating Actemra subcutaneous for giant cell arteritis (n = 251), patients were treated with corticosteroids in an open-label fashion (20 mg to 60 mg/day) during the screening period prior to treatment with Actemra subcutaneous.[2,3] Sustained remission at Week 52 was achieved in 56% of patients who received Actemra subcutaneous every week + 26-week prednisone taper and 53% of patients who received Actemra every other week + 26-week prednisone taper vs. 14% of patients in the 26-week prednisone taper and 18% of patients in the 52-week prednisone taper.
- **Interstitial Lung Disease Associated with Systemic Sclerosis:** EULAR guidelines for systemic sclerosis (2016) do not address Actemra.[14] In the pivotal trial evaluating Actemra subcutaneous for systemic sclerosis-associated interstitial lung disease, patients were required to have a percentage of predicted forced vital capacity (FVC% predicted) > 55%.[15] Among patients with interstitial lung disease confirmed on high-resolution computed tomography scan (n = 136), the change from baseline in FVC% predicted at Week 48 was significantly improved in the group taking Actemra (0.07 vs. -6.40 with placebo).
- **Polyarticular Juvenile Idiopathic Arthritis**: The American College of Rheumatology (ACR)/Arthritis Foundation guidelines for the treatment of Juvenile Idiopathic Arthritis (2019) are specific to juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis.[8] For patients without risk factors, initial therapy with a DMARD is conditionally recommended over a biologic (including Actemra). Biologics (e.g., Actemra) are conditionally recommended as initial treatment when combined with a DMARD over biologic monotherapy.
- **Rheumatoid Arthritis**: Guidelines from the ACR for the treatment of rheumatoid arthritis (2015) have tumor necrosis factor (TNF) inhibitors and non-TNF biologics (such as Actemra) equally

positioned as a recommended therapy following a trial of a conventional synthetic DMARD (e.g., methotrexate, leflunomide, hydroxychloroquine, sulfasalazine).[10]

- **Systemic Juvenile Idiopathic Arthritis**: The 2013 update of the 2011 ACR recommendations for the treatment of systemic juvenile idiopathic arthritis mention Actemra as a second- or third-line agent in patients with varying degrees of synovitis, with or without active systemic features.[9] Nonsteroidal anti-inflammatory drugs, systemic glucocorticoids, Kineret® (anakinra subcutaneous injection), TNF inhibitors, and methotrexate are among other treatment options.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Actemra subcutaneous. All approvals are provided for the approval duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of a patient treated with Actemra subcutaneous as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Actemra subcutaneous to be prescribed by or in consultation with a physician who specializes in the condition being treated.

All reviews for use of Actemra subcutaneous for COVID-19 and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Actemra subcutaneous is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Giant Cell Arteritis.** Approve for the duration noted if the patient meets ONE of the following criteria (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets BOTH of the following criteria (i and ii):
     - **i.** Patient has tried one systemic corticosteroid; AND
       Note: An example of a systemic corticosteroid is prednisone.
     - **ii.** The medication is prescribed by or in consultation with a rheumatologist.
   - **B)** Patient is Currently Receiving Actemra (Subcutaneous or Intravenous). Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):
     - **iii.** Patient has been established on therapy for at least 6 months; AND
       B) Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).
     - **iv.** Patient meets at least ONE of the following criteria (a or b):
       - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Actemra); OR
         C) Note: Examples of objective measures are serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), resolution of fever, and/or reduced dosage of corticosteroids.
       - **b)** Compared with baseline (prior to initiating Actemra), patient experienced an improvement in at least one symptom, such as decreased headache, scalp or jaw pain, decreased fatigue, and/or improved vision.

2. **Interstitial Lung Disease Associated with Systemic Sclerosis.** Approve for 1 year if the patient meets ONE of the following criteria (A or B):
   - **A)** Initial Therapy. Approve if the patient meets ALL of the following criteria (i, ii, iii, iv, and v):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has elevated acute phase reactants, defined as at least ONE of the following criteria (a, b, or c):
       - **a)** C-reactive protein (CRP) ≥ 6 mg/mL; OR
       - **b)** Erythrocyte sedimentation rate (ESR) ≥ 28 mm/h; OR
       - **c)** Platelet count ≥ 330 x 10^9/L; AND
     - **iii.** Forced vital capacity (FVC) is > 55% of the predicted value; AND
     - **iv.** Diagnosis is confirmed by high-resolution computed tomography; AND
     - **v.** The medication is prescribed by or in consultation with a pulmonologist or a rheumatologist.
   - **B)** Patient is Currently Receiving Actemra (Subcutaneous or Intravenous). Approve if the patient meets ALL of the following criteria (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has experienced a beneficial response to therapy over the previous 1 year while receiving Actemra; AND
       Note: For a patient who has received less than 1 year of therapy, response to therapy is from baseline prior to initiating Actemra. Examples of a beneficial response include a reduction in the anticipated decline in forced vital capacity, improvement in 6-minute walk distance, and/or reduction in the number or severity of disease-related exacerbations.
     - **iii.** The medication is prescribed by or in consultation with a pulmonologist or a rheumatologist.
3. **Polyarticular Juvenile Idiopathic Arthritis.** Approve for the duration noted if the patient meets ONE of the following criteria (A or B):
   - **D)** Initial Therapy. Approve for 6 months if the patient meets BOTH of the following criteria (i and ii):
     - **i.** Patient meets ONE of the following criteria (a, b, c, or d):
       - **e)** Patient has tried one other systemic therapy for this condition; OR
         Note: Examples of other systemic therapies include methotrexate, sulfasalazine, leflunomide, or a nonsteroidal anti-inflammatory drug (NSAID). A previous trial of one biologic other than the requested drug also counts as a trial of one systemic therapy for Juvenile Idiopathic Arthritis. A biosimilar of Actemra does not count. Refer to Appendix for examples of biologics used for Juvenile Idiopathic Arthritis.
       - **f)** Patient will be starting on Actemra subcutaneous concurrently with methotrexate, sulfasalazine, or leflunomide; OR
       - **g)** Patient has an absolute contraindication to methotrexate, sulfasalazine, or leflunomide; OR
         Note: Examples of absolute contraindications to methotrexate include pregnancy, breastfeeding, alcoholic liver disease, immunodeficiency syndrome, and blood dyscrasias; OR
       - **h)** Patient has aggressive disease, as determined by the prescriber; AND
     - **ii.** The medication is prescribed by or in consultation with a rheumatologist.
   - **B)** Patient is Currently Receiving Actemra (Subcutaneous or Intravenous). Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):
     - **i.** Patient has been established on therapy for at least 6 months; AND
       Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).
     - **i.** Patient meets at least ONE of the following criteria (a or b):
       - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Actemra); OR

Note: Examples of objective measures include Physician Global Assessment (MD global), Parent/Patient Global Assessment of Overall Well-Being (PGA), Parent/Patient Global Assessment of Disease Activity (PDA), Juvenile Arthritis Disease Activity Score (JDAS), Clinical Juvenile Arthritis Disease Activity Score (cJDAS), Juvenile Spondyloarthritis Disease Activity Index (JSpADA), serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating Actemra), patient experienced an improvement in at least one symptom, such as improvement in limitation of motion, less joint pain or tenderness, decreased duration of morning stiffness or fatigue, improved function or activities of daily living.

4. **Rheumatoid Arthritis.** Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following criteria (i and ii):

i. Patient has tried one conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND

Note: Examples of conventional DMARDs include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already had a 3-month trial with at least one biologic other than Actemra. A biosimilar of Actemra does not count. Refer to Appendix for examples of biologics used for rheumatoid arthritis. A patient who has already tried a biologic for rheumatoid arthritis is not required to "step back" and try a conventional synthetic DMARD.

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Actemra (Subcutaneous or Intravenous). Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):

ii. Patient has been established on therapy for at least 6 months; AND

E) Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

iii. Patient meets at least ONE of the following (a or b):

c) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR

Note: Examples of standardized and validated measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).

F) b) Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

5. **Systemic Juvenile Idiopathic Arthritis.** Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

C) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following criteria (i and ii):

i. Patient has tried one other systemic therapy for this condition; AND

Note: Examples of other systemic therapies include a corticosteroid (oral, intravenous), a conventional synthetic disease-modifying antirheumatic drug (DMARD) [e.g., methotrexate, leflunomide, sulfasalazine], or a 1-month trial of a nonsteroidal anti-inflammatory drug

(NSAID). A previous trial of one biologic other than Actemra (e.g., Kineret [anakinra subcutaneous injection], a tumor necrosis factor inhibitor [e.g., an etanercept product, an adalimumab product, an infliximab product], or Ilaris [canakinumab subcutaneous injection]) also counts towards a trial of one other systemic therapy for systemic juvenile idiopathic arthritis. A biosimilar of Actemra does not count.

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Actemra (Subcutaneous or Intravenous). Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least ONE of the following criteria (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

Other Uses with Supportive Evidence

6. Polymyalgia Rheumatica. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following criteria (i and ii):

i. Patient has tried one systemic corticosteroid; AND
Note: An example of a systemic corticosteroid is prednisone.

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Actemra (Subcutaneous or Intravenous). Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):

iii. Patient has been established on therapy for at least 6 months; AND
G) Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

iv. Patient meets at least ONE of the following criteria (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Actemra); OR
H) Note: Examples of objective measures are serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), resolution of fever, and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating Actemra), patient experienced an improvement in at least one symptom, such as decreased shoulder, neck, upper arm, hip, or thigh pain or stiffness; improved range of motion; and/or decreased fatigue.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Actemra subcutaneous is not recommended in the following situations:

1. **Concurrent use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Data that evaluate concomitant use of Actemra subcutaneous with another biologic or with a targeted synthetic DMARD for an inflammatory condition (see Appendix for examples) are lacking.[1,11] Combination therapy with biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher rate of adverse effects and lacks controlled trial data in support of additive efficacy.[12] Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Actemra subcutaneous.

2. **COVID-19 (Coronavirus Disease 2019).** Forward all requests to the Medical Director. Only Actemra intravenous is indicated for treatment of COVID-19 in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation.
   Note: This includes requests for cytokine release syndrome associated with COVID-19.

2. **Crohn's Disease.** In a 12-week pilot study conducted in Japan, 36 adults with active Crohn's disease (Crohn's Disease Activity Index [CDAI] ≥ 150 and increased C-reactive protein [CRP]) were randomized in a double-blind fashion to intravenous Actemra 8 mg/kg every 2 weeks, or alternating infusions of Actemra 8 mg/kg every 4 weeks and placebo (i.e., alternating with placebo every 2 weeks), or to placebo every 2 weeks.[13] At baseline, the mean CDAI ranged from 287 to 306. Patients had been treated with corticosteroids, mesalamine-type drugs, metronidazole, or elemental diet. Six patients in the placebo group, four on Actemra every 4 weeks, and one on Actemra every 2 weeks dropped out. The mean reduction in the CDAI score in the Actemra 8 mg/kg every 2 week group was 88 points – from (mean) 306 to 218. Further studies are needed.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

[*] Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARDs – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Adalimumab Products Prior Authorization Policy

- Abrilada™ (adalimumab-afzb subcutaneous injection – Pfizer)
- adalimumab-adaz subcutaneous injection (Sandoz/Novartis)
- adalimumab-fkjp subcutaneous injection (Mylan)
- Amjevita® (adalimumab-atto subcutaneous injection – Amgen)
- Cyltezo® (adalimumab-adbm subcutaneous injection – Boehringer Ingelheim)
- Hadlima™ (adalimumab-bwwd subcutaneous injection – Organon/Samsung Bioepis)
- Hulio® (adalimumab-fkjp subcutaneous injection – Mylan)
- Humira® (adalimumab subcutaneous injection – AbbVie)
- Hyrimoz® (adalimumab-adaz subcutaneous injection – Sandoz/Novartis)
- Idacio® (adalimumab-aacf subcutaneous injection – Fresenius Kabi)
- Yuflyma® (adalimumab-aaty subcutaneous injection – Celltrion)
- Yusimry™ (adalimuamb-aqvh subcutaneous injection – Coherus)

REVIEW DATE: 04/05/2023; selected revision 07/05/2023

OVERVIEW

Adalimumab products are tumor necrosis factor inhibitors (TNFis) approved for the following uses:[1]

- **Ankylosing spondylitis**, for reducing signs and symptoms in patients with active disease.
- **Crohn's disease**, for treatment of moderately to severely active disease in patients ≥ 6 years of age.
- **Hidradenitis suppurativa**, for the treatment of moderate to severe disease in patients ≥ 12 years of age.
- **Juvenile idiopathic arthritis (JIA)**, ± methotrexate for reducing signs and symptoms of moderately to severely active polyarticular disease in patients ≥ 2 years of age.
- **Plaque psoriasis**, for the treatment of adults with moderate to severe chronic disease who are candidates for systemic therapy or phototherapy and when other systemic therapies are medically less appropriate.
- **Psoriatic arthritis (PsA)**, ± conventional synthetic disease-modifying antirheumatic drugs (DMARDs), for reducing the signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function.
- **Rheumatoid arthritis**, ± methotrexate or other conventional synthetic DMARDS to reduce the signs and symptoms, induce major clinical response, inhibit the progression of structural damage, and improve physical function in adults with moderately to severely active disease.
- **Ulcerative colitis**, for treatment of moderately to severely active disease in patients ≥ 5 years of age. However, efficacy has not been established in patients with ulcerative colitis who have lost response or were intolerant to another TNFi.
- **Uveitis**, in patients ≥ 2 years of age with noninfectious intermediate, posterior, and panuveitis.

Guidelines

TNFis are featured prominently in guidelines for treatment of inflammatory conditions.

- **Ankylosing Spondylitis and Spondyloarthritis:** Guidelines for ankylosing spondylitis and non-radiographic axial spondylitis are published by the American College of Rheumatology (ACR)/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019).[3] TNFis are recommended as the initial biologic. In those who are secondary non-responders to a TNFi, a second TNFi is recommended over switching out of the class.

- **Crohn's Disease:** The American College of Gastroenterology (ACG) has guidelines for Crohn's disease (2018).[4] TNFis are listed as an option for disease that is resistant to corticosteroids, severely active disease, perianal fistulizing disease, and maintenance of remission. In post-operative Crohn's disease, a TNFi should be started within 4 weeks of surgery to prevent recurrence. Guidelines from the American Gastroenterological Association (AGA) [2021] include TNFis among the therapies for moderate to severe Crohn's disease, for induction and maintenance of remission.[17]
- **Hidradenitis Suppurativa:** British guidelines (2018) recommend consideration of adalimumab for those with moderate to severe disease who do not respond to conventional therapy.[19]
- **JIA:** There are guidelines from ACR and the Arthritis Foundation for the treatment of JIA (2021) which address oligoarthritis and temporomandibular joint (TMJ) arthritis. For oligoarthritis, a biologic is recommended following a trial of a conventional synthetic DMARD.[6] In patients with TMJ arthritis, scheduled nonsteroidal anti-inflammatory drugs (NSAIDs) and/or intra-articular glucocorticoids are recommended first-line. A biologic is a therapeutic option if there is an inadequate response or intolerance. Additionally, rapid escalation to a biologic ± conventional synthetic DMARD (methotrexate preferred) is often appropriate given the impact and destructive nature of TMJ arthritis. In these guidelines, there is not a preferred biologic that should be initiated for JIA. ACR guidelines (2019) are also available specifically for juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis.[5] TNFis are the biologics recommended for polyarthritis, sacroiliitis, and enthesitis. Biologics are recommended following other therapies (e.g., following DMARDs for active polyarthritis or following an NSAID for active JIA with sacroiliitis or enthesitis). However, there are situations where initial therapy with a biologic may be preferred over other conventional therapies (e.g., if there is involvement of high-risk joints such as the cervical spine, wrist, or hip; high disease activity; and/or those judged to be at high risk of disabling joint damage).
- **Plaque Psoriasis:** Guidelines from the American Academy of Dermatologists and National Psoriasis Foundation (2019) recommend adalimumab as a monotherapy treatment option for adults with moderate to severe disease.[7]
- **PsA:** Guidelines from ACR (2019) recommend TNFis over other biologics for use in treatment-naïve patients with PsA and in those who were previously treated with an oral therapy.[8]
- **Rheumatoid Arthritis:** Guidelines from ACR (2021) recommend addition of a biologic or a targeted synthetic DMARD for a patient taking the maximum tolerated dose of methotrexate who is not at target.[2]
- **Ulcerative Colitis:** Guidelines from the ACG for ulcerative colitis (2019) note that the following agents can be used for induction of remission in moderately to severely active disease: budesonide extended-release tablets, oral or intravenous systemic corticosteroids, Entyvio® (vedolizumab intravenous infusion), Xeljanz®/XR (tofacitinib tablets/extended-release tablets), or TNFis.[9] Guidelines from the AGA (2020) recommend Xeljanz only after failure of or intolerance to a TNFi.[10] In addition to the approved indication, clinical guidelines for the management of pouchitis (2009) indicate that first-line therapy for pouchitis is antibiotic therapy (e.g. metronidazole, ciprofloxacin).[11] Other treatment options include maintenance probiotics, oral or topical budesonide, anti-inflammatory drugs (e.g., mesalamine), or immunosuppressive agents (e.g., infliximab).
- **Uveitis and Ocular Inflammatory Disorders:** American Academy of Ophthalmology (AAO) guidelines (2014) note that adalimumab may be used in patients with uveitis due to various causes (e.g., spondyloarthropathy-associated or human leukocyte antigen [HLA]-B27-associated uveitis, JIA-associated uveitis, and other posterior uveitides and panuveitis syndromes).[12] Adalimumab should be considered second-line in vision-threatening JIA-associated uveitis when methotrexate has failed or is not tolerated (strong recommendation) and may be used as corticosteroid-sparing treatment for vision-threatening chronic uveitis from seronegative spondyloarthropathy (strong

recommendation). Adalimumab may also be considered in other patients who have vision-threatening or corticosteroid-dependent disease who have failed first-line therapies. Adalimumab should be considered as a second-line immunomodulatory agent for severe ocular inflammatory conditions including chronic and severe scleritis. ACR/Arthritis Federation guidelines (2019) for uveitis associated with JIA make recommendations for use of conventional systemic DMARDs and biologics. In patients with severe active chronic anterior uveitis associated with sight-threatening complications, a TNFi (monoclonal antibody) + methotrexate is recommended.[19]

Other Uses with Supportive Evidence

1. There are guidelines and/or published data supporting the use of adalimumab products in the following conditions:

- **Behcet's Disease:** The European Union Against Rheumatism (EULAR) recommendations (2018) include TNFis for initial or recurrent sight-threatening uveitis.[13] For patients refractory to first-line treatments (e.g., corticosteroids), TNFis are among the treatment options for mucocutaneous manifestations, venous thrombosis, severe or refractory gastrointestinal disease, and recurrent/chronic joint involvement. Recommendations for the use of TNFis in ocular inflammatory disorders from the AAO (2014) note that TNFis may be used first-line in patients with ophthalmic manifestations of Behcet's disease and for acute exacerbations of preexisting Behcet's disease.[12]
- **Pyoderma Gangrenosum:** Although guidelines are not current, multiple topical and systemic therapies have been used for pyoderma gangrenosum. Oral prednisone is the most common initial immunosuppressant medication.[14] Other systemic therapies include cyclosporine, methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, and TNFis (i.e., infliximab, etanercept, and adalimumab products). In case reports, TNFis have been effective.
- **Sarcoidosis:** According to European Respiratory Society guidelines for sarcoidosis (2021), a TNFi is recommended after a trial of glucocorticoids and immunosuppressants for pulmonary and neurosarcoidosis.[15]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of adalimumab products. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with adalimumab products as well as the monitoring required for adverse events and long-term efficacy, initial approval requires the agent to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of adalimumab products is recommended in those who meet one the following criteria:

FDA-Approved Indications

I) Ankylosing Spondylitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Adalimumab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with an adalimumab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

1. When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an adalimumab product); OR
Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondyloarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

2. Compared with baseline (prior to initiating an adalimumab product), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

J) Crohn's Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, and iii):

i. Patient is ≥ 6 years of age; AND

ii. Patient meets ONE of the following (a, b, c, or d):

1. Patient has tried or is currently taking corticosteroids, or corticosteroids are contraindicated in this patient; OR
Note: Examples of corticosteroids are prednisone or methylprednisolone.

2. Patient has tried one other conventional systemic therapy for Crohn's disease; OR
Note: Examples of conventional systemic therapy for Crohn's disease include azathioprine, 6-mercaptopurine, or methotrexate. An exception to the requirement for a trial of or contraindication to steroids or a trial of one other conventional systemic agent can be made if the patient has already tried at least one biologic other than the requested medication. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for Crohn's disease. A trial of mesalamine does not count as a systemic agent for Crohn's disease.

3. Patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas; OR

4. Patient had ileocolonic resection (to reduce the chance of Crohn's disease recurrence); AND

iii. The medication is prescribed by or in consultation with a gastroenterologist.

B) Patient is Currently Receiving an Adalimumab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with an adalimumab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an adalimumab product); OR

K) Note: Examples of objective measures include fecal markers (e.g., fecal lactoferrin, fecal calprotectin), serum markers (e.g., C-reactive protein), imaging studies (magnetic resonance enterography [MRE], computed tomography enterography [CTE]), endoscopic assessment, and/or reduced dose of corticosteroids.

b) Compared with baseline (prior to initiating an adalimumab product), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or blood in stool.

L) Juvenile Idiopathic Arthritis (JIA) [or juvenile rheumatoid arthritis] {regardless of type of onset}. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):
Note: This includes a patient with juvenile spondyloarthropathy/active sacroiliac arthritis.

A) Initial Therapy. Approve for 6 months if the patient meets the following (i and ii):

i. Patient meets ONE of the following (a, b, c, or d):

a) Patient has tried one other systemic therapy for this condition; OR

2. Note: Examples of other systemic therapies for JIA include methotrexate, sulfasalazine, leflunomide, or a nonsteroidal anti-inflammatory drug (NSAID) [e.g., ibuprofen, naproxen]. A previous trial of one biologic other than the requested medication also counts as a trial of one systemic therapy for JIA. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for JIA.

b) Patient will be starting on adalimumab concurrently with methotrexate, sulfasalazine, or leflunomide; OR

c) Patient has an absolute contraindication to methotrexate, sulfasalazine, or leflunomide; OR

3. Note: Examples of contraindications to methotrexate include pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, blood dyscrasias.

d) Patient has aggressive disease, as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Adalimumab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with an adalimumab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an adalimumab product); OR
Note: Examples of objective measures include Physician Global Assessment (MD global), Parent/Patient Global Assessment of Overall Well-Being (PGA), Parent/Patient Global Assessment of Disease Activity (PDA), Juvenile Arthritis Disease Activity Score (JDAS), Clinical Juvenile Arthritis Disease Activity Score (cJDAS), Juvenile Spondyloarthritis Disease Activity Index (JSpADA), serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

c) Compared with baseline (prior to initiating an adalimumab product), patient experienced an improvement in at least one symptom, such as improvement in limitation of motion, less joint pain or tenderness, decreased duration of morning stiffness or fatigue, or improved function or activities of daily living.

4.

M) Hidradenitis Suppurativa. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patients meets BOTH of the following (i and ii):

i. Patient has tried at least ONE other therapy; AND
Note: Examples include intralesional or oral corticosteroids (such as triamcinolone or prednisone), systemic antibiotics (e.g., clindamycin, dicloxacillin, or erythromycin), or isotretinoin.

ii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving an Adalimumab Product. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has been established on therapy for at least 90 days; AND

N) Note: A patient who has received < 90 days of therapy or who is restarting therapy with an adalimumab product is reviewed under criterion A (Initial Therapy).

ii. When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an adalimumab product); AND

O) Note: Examples of objective measures include Hurley staging, Sartorius score, Physician Global Assessment, and Hidradenitis Suppurativa Severity Index.

iii. Compared with baseline (prior to initiating an adalimumab product), patient experienced an improvement in at least one symptom, such as decreased pain or drainage of lesions, nodules, or cysts.

5.

P) **Plaque Psoriasis.** Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets ONE of the following conditions (a or b):

1. Patient has tried at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR

Note: Examples include methotrexate, cyclosporine, acitretin, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already had a 3-month trial or previous intolerance to at least one biologic other than the requested medication. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for psoriasis. A patient who has already tried a biologic for psoriasis is not required to "step back" and try a traditional systemic agent for psoriasis.

b) Patient has a contraindication to methotrexate, as determined by the prescriber; AND

iii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving an Adalimumab Product. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has been established on therapy for at least 90 days; AND

Note: A patient who has received < 90 days of therapy or who is restarting therapy with an adalimumab product is reviewed under criterion A (Initial Therapy).

ii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating an adalimumab product) in at least one of the following: estimated body surface area affected, erythema, induration/thickness, and/or scale of areas affected by psoriasis; AND

iii. Compared with baseline (prior to receiving an adalimumab product), patient experienced an improvement in at least one symptom, such as decreased pain, itching, and/or burning.

Q)

R) **Psoriatic Arthritis.** Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving an Adalimumab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with an adalimumab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following criteria (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an adalimumab product); OR

S) Note: Examples of objective measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsA DAS), Grace Index, Leeds Enthesitis Score (LEI), Spondyloarthritis Consortium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating an adalimumab product), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; or decreased soft tissue swelling in joints or tendon sheaths.

T) Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND

Note: Examples include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already had a 3-month trial with at least one biologic other than the requested medication. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for rheumatoid arthritis. A patient who has already tried a biologic for rheumatoid arthritis is not required to "step back" and try a conventional synthetic DMARD.

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Adalimumab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

iii. Patient has been established on therapy for at least 6 months; AND

U) Note: A patient who has received < 6 months of therapy or who is restarting therapy with an adalimumab product is reviewed under criterion A (Initial Therapy).

iv. Patient meets at least one of the following (a or b):

d) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR

Note: Examples of objective measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate or C-reactive protein, Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).

V) b) Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; or decreased soft tissue swelling in joints or tendon sheaths.

8. Ulcerative Colitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, and iii):

i. Patient is ≥ 5 years of age; AND

ii. Patient meets ONE of the following (a or b):

a) Patient has tried one systemic therapy; OR

Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone or methylprednisolone. A trial of one biologic other than the requested medication also counts as a trial of one systemic agent for ulcerative colitis. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for ulcerative colitis.

b) Patient meets BOTH of the following [(1) and (2)]:

(1) Patient has pouchitis; AND

(2) Patient has tried an antibiotic, probiotic, corticosteroid enema, or mesalamine enema; AND

Note: Examples of antibiotics include metronidazole and ciprofloxacin. Examples of corticosteroid enemas include hydrocortisone enema.

iii. The medication is prescribed by or in consultation with a gastroenterologist.

B) Patient is Currently Receiving an Adalimumab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND

W) Note: A patient who has received < 6 months of therapy or who is restarting therapy with an adalimumab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an adalimumab product); OR

X) Note: Examples of objective measures include fecal markers (e.g., fecal calprotectin), serum markers (e.g., C-reactive protein), endoscopic assessment, and/or reduced dose of corticosteroids.

b) Compared with baseline (prior to initiating an adalimumab product), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or rectal bleeding.

Y)

Z) Uveitis (including other posterior uveitides and panuveitis syndromes). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i and ii):

i. Patient has tried ONE of the following therapies: periocular, intraocular, or systemic corticosteroids; immunosuppressives; AND

Note: Examples of corticosteroids include prednisolone, triamcinolone, betamethasone, methylprednisolone, and prednisone. Examples of immunosuppressive agents include methotrexate, mycophenolate mofetil, azathioprine, and cyclosporine. A trial of one biologic other than the requested medication also counts. A biosimilar of the requested biologic does not count.

ii. The medication is prescribed by or in consultation with an ophthalmologist.

B) Patient is Currently Receiving an Adalimumab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with an adalimumab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an adalimumab product); OR

AA) Note: Examples of objective measures include best-corrected visual acuity, assessment of chorioretinal and/or inflammatory retinal vascular lesions, or anterior chamber cell grade or vitreous haze grade.

b) Compared with baseline (prior to initiating an adalimumab product), patient experienced an improvement in at least one symptom, such as decreased eye pain, redness, light sensitivity, and/or blurred vision; or improvement in visual acuity.

Other Uses with Supportive Evidence

BB) Behcet's Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii):

i. Patient meets ONE of the following (a or b):

a) Patient has tried at least ONE conventional therapy; OR

6. Note: Examples include systemic corticosteroids (e.g., methylprednisolone), immunosuppressants (e.g., azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, tacrolimus, Leukeran [chlorambucil tablets], cyclophosphamide, interferon alfa). A trial of one biologic other than the requested medication also counts. A patient who has already tried one biologic other than the requested drug for Behcet's disease is not required to "step back" and try a conventional therapy. A biosimilar of the requested biologic does not count.

b) Patient has ophthalmic manifestations of Behcet's disease; AND

ii. The medication is prescribed by or in consultation with a rheumatologist, dermatologist, ophthalmologist, gastroenterologist, or neurologist.

B) Patient is Currently Receiving an Adalimumab Product. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has been established on therapy for at least 90 days; AND

CC) Note: A patient who has received < 90 days of therapy or who is restarting therapy with an adalimumab product is reviewed under criterion A (Initial Therapy).

ii. When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an adalimumab product); AND

DD) Note: Examples of objective measures are dependent upon organ involvement but may include best-corrected visual acuity (if ophthalmic manifestations); serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate); or ulcer depth, number, and/or lesion size.

iii. Compared with baseline (prior to initiating an adalimumab product), patient experienced an improvement in at least one symptom, such as decreased pain or improved visual acuity (if ophthalmic manifestations).

EE) Pyoderma Gangrenosum. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets BOTH of the following (i and ii):

i. Patient meets ONE of the following (a or b):

a) Patient has tried one systemic corticosteroid; OR

Note: An example is prednisone.

b) Patient has tried one other immunosuppressant for at least 2 months or was intolerant to one of these agents; AND

Note: Examples include mycophenolate mofetil and cyclosporine.

ii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving an Adalimumab Product. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has been established on therapy for at least 4 months; AND

FF) Note: A patient who has received < 4 months of therapy or who is restarting therapy with an adalimumab product is reviewed under criterion A (Initial Therapy).

ii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating an adalimumab product) in at least one of the following: size, depth, and/or number of lesions; AND

iii. Compared with baseline (prior to initiating an adalimumab product), patient experienced an improvement in at least one symptom, such as decreased pain and/or tenderness of affected lesions.

GG) Sarcoidosis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient has tried at least one corticosteroid; AND
Note: An example is prednisone.

ii. Patient has tried at least one immunosuppressive medication; AND
Note: Examples include methotrexate, leflunomide, azathioprine, mycophenolate mofetil, cyclosporine, Leukeran (chlorambucil tablets), cyclophosphamide, Thalomid (thalidomide capsules), an infliximab product, or chloroquine.

iii. The medication is prescribed by or in consultation with a pulmonologist, ophthalmologist, or dermatologist.

B) Patient is Currently Receiving an Adalimumab Product. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has been established on therapy for at least 90 days; AND
HH) Note: A patient who has received < 90 days of therapy or who is restarting therapy with an adalimumab product is reviewed under criterion A (Initial Therapy).

ii. When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an adalimumab product); AND
II) Note: Examples of objective measures are dependent upon organ involvement but may include lung function (e.g., predicted forced vital capacity and/or 6-minute walk distance); serum markers (e.g., C-reactive protein, liver enzymes, N-terminal pro-brain natriuretic peptide [NT-proBNP]); improvement in rash or skin manifestations, neurologic symptoms, or rhythm control; or imaging (e.g., if indicated, chest radiograph, magnetic resonance imaging [MRI], or echocardiography).

iii. Compared with baseline (prior to initiating an adalimumab product), patient experienced an improvement in at least one symptom, such as decreased cough, fatigue, pain, palpitations, neurologic symptoms, and/or shortness of breath.

JJ) Scleritis or Sterile Corneal Ulceration. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient has tried one other therapy for this condition; AND
Note: Examples include oral nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin, naproxen, or ibuprofen; oral, topical (ophthalmic), or intravenous corticosteroids (such as prednisone, prednisolone, methylprednisolone); methotrexate; cyclosporine; or other immunosupressants.

ii. The medication is prescribed by or in consultation with an ophthalmologist.

B) Patient is Currently Receiving an Adalimumab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with an adalimumab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an adalimumab product); OR

KK) Note: Examples of objective measures are serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating an adalimumab product), patient experienced an improvement in at least one symptom, such as decreased eye pain, redness, light sensitivity, tearing, and/or improvement in visual acuity.

LL) Spondyloarthritis, Other Subtypes. Approve for the duration noted if the patient meets ONE of the following (A or B):

MM) Note: This includes undifferentiated arthritis, non-radiographic axial spondyloarthritis, reactive arthritis (Reiter's disease), or arthritis associated with inflammatory bowel disease. For ankylosing spondylitis or psoriatic arthritis, refer to the respective criteria under FDA-approved indications.

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient meets one of the following (a or b):

a) Patient meets both of the following [(1) and (2)]:

(1) Patient has arthritis primarily in the knees, ankles, elbows, wrists, hands, and/or feet; AND

(2) Patient has tried at least one conventional synthetic disease-modifying antirheumatic drug (DMARD); OR

NN) Note: Examples include methotrexate, leflunomide, or sulfasalazine.

b) Patient has axial spondyloarthritis AND has objective signs of inflammation, defined as at least one of the following [(1) or (2)]:

(1) C-reactive protein elevated beyond the upper limit of normal for the reporting laboratory; OR

(2) Sacroiliitis reported on magnetic resonance imaging (MRI); AND

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Adalimumab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with an adalimumab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an adalimumab product); OR

Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS) and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating an adalimumab product), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of adalimumab products is not recommended in the following situations:

7.

1. Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD). An adalimumab product should not be administered in combination with another

biologic or with a targeted synthetic DMARD used for an inflammatory condition (see Appendix for examples). Combination therapy is generally not recommended due to a potentially higher rate of adverse events with combinations and lack of data supportive of additional efficacy.
~~8.~~ Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine) in combination with an adalimumab product.

2. **Polymyalgia Rheumatica (PMR).** EULAR/ACR guidelines for the management of PMR (2015) strongly recommend against the use of tumor necrosis factor inhibitors (TNFis) for treatment of PMR.[17] This recommendation is based on lack of evidence for benefit as well as considerable potential for harm.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

[*] Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Arcalyst Prior Authorization Policy
- Arcalyst® (rilonacept subcutaneous injection – Regeneron)

REVIEW DATE: 01/25/2023

OVERVIEW

Arcalyst, an interleukin-1 blocker, is indicated for the following uses:[1]

- **Cryopyrin-associated periodic syndromes (CAPS)**, including familial cold autoinflammatory syndrome and Muckle-Wells syndrome, for treatment of patients ≥ 12 years of age.
- **Deficiency of interleukin-1 receptor antagonist (DIRA),** for maintenance of remission in patients weighing at least 10 kg.
- **Pericarditis**, for treatment of recurrent disease and reduction in risk of recurrence in patients ≥ 12 years of age.

In the pivotal trial for CAPS, patients had significant improvement in symptom scores with Arcalyst through Week 6 which were maintained through Week 15. The pivotal trial for DIRA enrolled patients with a loss of function *IL1RN* mutation who previously experienced a benefit with Kineret® (anakinra subcutaneous injection). All patients (n = 6) were in remission at Month 6 and sustained remission for the remainder of the 2-year study. In the pivotal trial for pericarditis, patients had a mean of 4.7 total episodes of pericarditis (standard deviation, ± 1.7 episodes), including the current episode. All patients who enrolled in the study were symptomatic despite treatment with standard treatment (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], colchicine, and/or systemic corticosteroids). Patients who responded to Arcalyst during the initial 12 weeks of treatment, defined as C-reactive protein ≤ 0.5 mg/dL with minimal or no pain (daily rating pain score), were eligible for continuation in the randomized withdrawal period.

Guidelines

Pericarditis

Guidelines for acute and chronic pericarditis are available from the American College of Cardiology (2020).[2] Asymptom-free interval of 4 to 6 weeks and evidence of new pericardial inflammation are needed for a diagnosis of recurrent disease. For recurrent disease, controlled clinical trials support a remarkable reduction in recurrences with colchicine, which should be continued for at least 6 months. Additionally, low-dose corticosteroids are associated with a high treatment success rate. NSAIDs (e.g., aspirin, ibuprofen, indomethacin) are also listed as alternatives for recurrent disease. Immunosuppressive drugs, including azathioprine, methotrexate, and mycophenolate mofetil, are effective, well tolerated, and used as corticosteroid-sparing agents. There is also limited evidence suggesting efficacy of intravenous immunoglobulins. Although Arcalyst was not yet approved for recurrent pericarditis, the guidelines note that benefit was shown in a Phase II study, demonstrated by a decrease in chest pain and C-reactive protein levels.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Arcalyst. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Arcalyst as well as the monitoring required for adverse events and long-term efficacy, initial approval

requires Arcalyst to be prescribed by or in consultation with a physician who specializes in the condition being treated.

All reviews for use of Arcalyst for COVID-19 and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Arcalyst is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Cryopyrin-Associated Periodic Syndromes.** Approve for the duration noted if the patient meets one of the following (A or B):
   Note: This includes familial cold autoinflammatory syndrome, Muckle-Wells Syndrome, and neonatal onset multisystem inflammatory disease or chronic infantile neurological cutaneous and articular syndrome.
   A) Initial Therapy. Approve for 6 months if the patient meets the following conditions (i and ii):
      i. Patient is ≥ 12 years of age; AND
      ii. The medication is prescribed by or in consultation with a rheumatologist, geneticist, allergist/immunologist, or dermatologist.
   B) Patient is Currently Receiving Arcalyst. Approve for 1 year if the patient meets BOTH of the following (i and ii):
      i. Patient has been established on this medication for at least 6 months; AND
      Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).
      ii. Patient meets at least one of the following (a or b):
         a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
         Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, amyloid A), reduction in proteinuria, and/or stabilization of serum creatinine.
         b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as fewer cold-induced attacks; less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

2. **Deficiency of Interleukin-1 Receptor Antagonist**. Approve for the duration noted if the patient meets one of the following (A or B):
   A) Initial Therapy. Approve for 6 months if the patient meets all of the following (i, ii, iii, and iv):
   i. Patient is ≥ 10 kg (22 pounds); AND
   ii. Genetic testing has confirmed a mutation in the *IL1RN* gene; AND
   iii. According to the prescriber, patient has demonstrated a clinical benefit with Kineret (anakinra subcutaneous injection); AND
      i. Note: Examples of a clinical response with Kineret include normalized acute phase reactants; resolution of fever, skin rash, and bone pain; and reduced dosage of corticosteroids.

iv. The medication is prescribed by or in consultation with a rheumatologist, geneticist, dermatologist, or a physician specializing in the treatment of autoinflammatory disorders.

B) Patient is Currently Receiving Arcalyst. Approve for 1 year if the patient meets BOTH of the following (i and ii):

ii. Patient has been established on this medication for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

iii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR

Note: Examples of objective measures include improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), reduction in proteinuria, and/or stabilization of serum creatinine.

iv. b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as improvement of skin or bone symptoms; less joint pain/tenderness, stiffness, or swelling.

v.

3. Pericarditis. Approve for the duration noted if the patient meets one of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets all of the following (i, ii, iii, iv, and v):

i. Patient is ≥ 12 years of age; AND

ii. Patient has recurrent pericarditis; AND

iii. Prior to starting treatment with Arcalyst, the patient had a of at least three episodes of pericarditis; AND

iv. Patient meets one of the following (a or b):

a) For the current episode, the patient is receiving standard treatment; OR

b) Standard treatment is contraindicated; AND

vi. Note: Standard treatments for pericarditis include nonsteroidal anti-inflammatory drug(s) [NSAIDs], colchicine, and/or systemic corticosteroids.

v. The medication is prescribed by or in consultation with a cardiologist or rheumatologist.

B) Patient is Currently Receiving Arcalyst. Approve for 1 year if the meets BOTH of the following (i and ii):

vii. i. Patient has been established on this medication for at least 3 months; AND

Note: A patient who has received < 90 days of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

viii.ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR

Note: Examples of objective measures include normalization of inflammatory biomarkers such as erythrocyte sedimentation rate and/or C-reactive protein, continued resolution of fever.

ix. b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as resolution of chest pain or pericarditis pain.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Arcalyst is not recommended in the following situations:

89. Concurrent Biologic Therapy. Arcalyst should not be administered in combination with another biologic agent for an inflammatory condition (see Appendix for examples).[1] Arcalyst has not been used in combination with tumor necrosis factor inhibitors (TNFis). An increased incidence of serious infections has been associated with another interleukin-1 blocker (Kineret® [anakinra subcutaneous injection]) when given in combination with TNFis.

90. COVID-19 (Coronavirus Disease 2019). Forward all requests to the Medical Director.
Note: This includes requests for cytokine release syndrome associated with COVID-19.

91. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Arcalyst® subcutaneous injection [prescribing information]. Tarrytown, NY: Regeneron; March 2021.
2. Chiabrando JG, Bonaventura A, Vecchie A, et al. Management of acute and recurrent pericarditis. *J Am Coll Cardiol.* 2020;75(1):76-92.
3. Klein AL, Imazio M, Cremer P, et al. Phase 3 trial of interleukin-1 trap rilonacept in recurrent pericarditis. *N Engl J Med.* 2021;384(1):31-41.

APPENDIX

[*] Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Bimzelx Prior Authorization Policy
- Bimzelx® (bimekizumab-bkzx subcutaneous injection – UCB)

REVIEW DATE: 11/01/2023

OVERVIEW
Bimzelx, an interleukin (IL)-17A and IL-17F blocker, is indicated for treatment of adults with moderate to severe **plaque psoriasis** who are candidates for systemic therapy or phototherapy.[1]

Guidelines
Bimzelx is not addressed in available guidelines. Guidelines for the treatment of psoriasis with biologics from the American Academy of Dermatologists and National Psoriasis Foundation (2019) list the approved biologics that may be used as monotherapy for adults with moderate to severe disease.[3]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Bimzelx. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Bimzelx as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Bimzelx to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Bimzelx is recommended in those who meet the following criteria:

FDA-Approved Indication

OO) Plaque Psoriasis. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):
- **A)** Initial Therapy. Approve for 3 months if the patient meets ALL of the following criteria (i, ii, and iii):
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** Patient meets ONE of the following conditions (a or b):
    - **a)** Patient has tried at least at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR
      Note: Examples include methotrexate, cyclosporine, acitretin, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already had a 3-month trial or previous intolerance to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for plaque psoriasis. A patient who has already tried a biologic for psoriasis is not required to "step back" and try a traditional systemic agent for psoriasis.

b) Patient has a contraindication to methotrexate, as determined by the prescriber; AND

iii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Bimzelx. Approve for 1 year if the patient meets ALL of the following criteria (i, ii, and iii):

i. Patient has been established on therapy for at least 90 days; AND
Note: A patient who has received < 90 days of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating Bimzelx) in at least one of the following: estimated body surface area, erythema, induration/thickness, and/or scale of areas affected by psoriasis; AND

iii. Compared with baseline (prior to receiving Bimzelx), patient experienced an improvement in at least one symptom, such as decreased pain, itching, and/or burning.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Bimzelx is not recommended in the following situations:

•

92. Concurrent Use with other Biologics or with Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs). Bimzelx should not be administered in combination with a biologic used for an inflammatory condition (see Appendix for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMRADs has a potential for a higher rate of adverse effects and lacks controlled trial data in support of additive efficacy.
Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Bimzelx.

93. Inflammatory Bowel Disease (i.e., Crohn's disease, ulcerative colitis). Exacerbations of inflammatory bowel disease, in some cases serious, occurred in clinical trials involving patients treated with Bimzelx.[1]

94. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

285. Bimzelx® subcutaneous injection [prescribing information]. Smyrna, GA: UCB; October 2023.
286. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2019 80(4):1029-1072.

APPENDIX

[*] Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; PMR – Polymyalgia rheumatic; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Cibinqo Prior Authorization Policy
- Cibinqo® (abrocitinib tablets – Pfizer)

REVIEW DATE: 02/15/2023

OVERVIEW

Cibinqo, a Janus kinase inhibitor (JAKi), is indicated for treatment of refractory, moderate to severe **atopic dermatitis** in patients ≥ 12 years of age whose disease is not adequately controlled with other systemic drug products (including biologics) or when those therapies are not advisable.[1] Cibinqo is not recommended for use in combination with other JAKis, biologic immunomodulators, or with other immunosuppressants.

Guidelines

US-based atopic dermatitis guidelines do not address Cibinqo.[2-4] Phototherapy, followed by systemic therapy, is generally used if initial topical treatments have failed to adequately control the signs and symptoms of disease.[2,4] A variety of systemic agents have been used off-label for treatment of atopic dermatitis, including cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. Biological guidelines from the European Academy of Allergy and Clinical Immunology (2021) also do not address Cibinqo.[5,6] Dupixent® (dupilumab subcutaneous injection) is recommended for use in patients ≥ 6 years of age with atopic dermatitis not adequately controlled with topical prescription therapies or when those therapies are not advisable (moderate to severe disease in patients ≥ 12 years of age; severe disease in patients 6 to 11 years of age).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cibinqo. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cibinqo as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Cibinqo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

All reviews for use of Cibinqo for COVID-19 and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cibinqo is recommended in those who meet the following criteria:

FDA-Approved Indication

7. Atopic Dermatitis. Approve for the duration noted if the patient meets one of the following (A or B):
23. Initial Therapy. Approve for 3 months if the patient meets the following criteria (i, ii, and iii):
i. Patient is ≥ 12 years of age; AND

ii. Patient meets one of the following (a or b):
- **a)** Patient has had a 3-month trial of at least ONE traditional systemic therapy; OR
- **b)** Patient has tried at least ONE traditional systemic therapy but was unable to tolerate a 3-month trial; AND

  Note: Examples of traditional systemic therapies include methotrexate, azathioprine, cyclosporine, and mycophenolate mofetil. A patient who has already tried Dupixent (dupilumab subcutaneous injection) or Adbry (tralokinumab-ldrm subcutaneous injection) is not required to "step back" and try a traditional systemic agent for atopic dermatitis.

iii. The medication is prescribed by or in consultation with an allergist, immunologist, or dermatologist.

24. Patient is Currently Receiving Cibinqo. Approve for 1 year if the patient meets the following (i, ii, and iii):
- **i.** Patient has already received at least 90 days of therapy with Cibinqo; AND

  Note: A patient who has received < 90 days of therapy or who is restarting therapy with Cibinqo should be considered under Initial Therapy.
- **ii.** Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating Cibinqo) in at least one of the following: estimated body surface area affected, erythema, induration/papulation/edema, excoriations, lichenification, and/or a decreased requirement for other topical or systemic therapies for atopic dermatitis; AND
- **iii.** Compared with baseline (prior to receiving Cibinqo), patient experienced an improvement in at least one symptom, such as decreased itching.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cibinqo is not recommended in the following situations:

95. Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD). Cibinqo is not recommended in combination with biologic immunomodulators or with other immunosuppressants such as those used for inflammatory conditions (see Appendix for examples).[1]

96. Concurrent Use with a Biologic Immunomodulator. Cibinqo is not recommended in combination with biologic immunomodulators.[1]

Note: Examples include Adbry (tralokinumab-ldrm subcutaneous injection), Cinqair (reslizumab intravenous), Dupixent (dupilumab subcutaneous injection), Fasenra (benralizumab subcutaneous injection), Nucala (mepolizumab subcutaneous injection), Tezspire (tezepelumab-ekko subcutaneous injection), and Xolair (omalizumab subcutaneous injection).

97. Concurrent Use with Other Janus Kinase Inhibitors (JAKis). Cibinqo is not recommended in combination with other JAKis, such as Rinvoq (upadacitinib tablets), Xeljanz/XR (tofacitinib tablets/extended-release tablets), Olumiant (baricitinib tablets).[1]

VV)

98. Concurrent Use with Other Potent Immunosuppressants (e.g., azathioprine, cyclosporine).[1] Coadministration with other potent immunosuppressive drugs has the risk of added immunosuppression and has not been evaluated.

WW)

99. COVID-19 (Coronavirus Disease 2019). Forward all requests to the Medical Director.

Note: This includes requests for cytokine release syndrome associated with COVID-19.

100. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

272. Cibinqo® tablets [prescribing information]. New York, NY: Pfizer; February 2023.
273. Schneider L, Tilles S, Lio P, et al. Atopic dermatitis: a practice parameter update 2012. *J Allergy Clin Immunol.* 2013;131:295-299.
274. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis. Section 2: management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol*. 2014;71(1):116-132.
275. Sidbury R, et al. Guidelines of care for the management of atopic dermatitis Section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol*. 2014;71(2):327-349.
276. Agache I, Akdis CA, Akdis M, et al. EAACI biologicals guidelines-dupilumab for children and adults with moderate to severe atopic dermatitis. *Allergy*. 2021;76(4):988-1009.
277. Wollenberg A, Christen-Zach S, Taieb A, et al. ETFAD/EADV eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children. *J Eur Acad Dermatol Venereol*. 2020;34(12):2717-2744.

APPENDIX

[*] Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Cimzia Prior Authorization Policy
- Cimzia® (certolizumab pegol subcutaneous injection [lyophilized powder or solution] – UCB)

REVIEW DATE: 04/05/2023

OVERVIEW

Cimzia, a tumor necrosis factor inhibitor (TNFi), is indicated for the following uses:[1]
- **Ankylosing spondylitis**, for the treatment of adults with active disease.
- **Crohn's disease**, for reducing signs and symptoms and maintaining clinical responses in adults with moderate to severe active disease who have had an inadequate response to conventional therapy.
- **Non-radiographic axial spondyloarthritis**, in patients with objective signs of inflammation.
- **Plaque psoriasis**, for the treatment of adults with moderately to severely active disease who are candidates for systemic therapy or phototherapy.
- **Psoriatic arthritis**, for the treatment of adult patients with active disease.
- **Rheumatoid arthritis**, for the treatment of adults with moderately to severely active disease.

Cimzia may be used as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).

Guidelines

TNFis feature prominently in guidelines for treatment of inflammatory conditions.
- **Axial Spondyloarthritis and Spondyloarthritis:** Guidelines for ankylosing spondylitis and non-radiographic axial spondyloarthritis are published by the ACR/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019).[2] TNFis are recommended for the initial biologic. In those who are secondary nonresponders to a TNFi, a second TNFi is recommended over switching out of the class.
- **Crohn's Disease:** The American College of Gastroenterology has guidelines for Crohn's disease (2018).[3] TNFis are listed as an option for disease that is resistant to corticosteroids, severely active disease, perianal fistulizing disease, and maintenance of remission. In post-operative Crohn's disease, a TNFi should be started within 4 weeks of surgery to prevent recurrence. Guidelines from the American Gastroenterological Association (2021) include TNFis among the therapies for moderate to severe Crohn's disease, for induction and maintenance of remission.[7]
- **Plaque Psoriasis:** Guidelines from the American Academy of Dermatologists and National Psoriasis Foundation (2019) recommend TNFis as a monotherapy treatment option for adults with moderate to severe disease.[4] Based on extrapolation of data, Cimzia is likely to have class characteristics similar to the other TNFis.
- **Psoriatic Arthritis:** Guidelines from ACR (2018) generally recommend treatment with a TNFi over other therapies as initial treatment for patients who are treatment-naïve.[5]
- **Rheumatoid Arthritis:** Guidelines from ACR (2021) recommend addition of a biologic or a targeted synthetic disease modifying anti-rheumatic drug (DMARD) for a patient taking the maximum tolerated dose of methotrexate who is not at target.[6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cimzia. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cimzia as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Cimzia to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

FDA-Approved Indications

1. **Ankylosing Spondylitis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist.
   - **B)** Patient is Currently Receiving Cimzia. Approve for 1 year if the patient meets BOTH of the following (i and ii):
     - **i.** Patient has been established on therapy for at least 6 months; AND
       Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).
     - **ii.** Patient meets at least one of the following (a or b):
       - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
         Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondylarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).
       - **b)** Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.
         A)
2. **Crohn's Disease.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **B)** Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient meets one of the following (a, b, c, or d):
       - **a)** Patient has tried or is currently taking corticosteroids, or corticosteroids are contraindicated in this patient; OR
       - **b)** Patient has tried one other conventional systemic therapy for Crohn's disease; OR
         C) Note: Examples of systemic therapies for Crohn's disease include azathioprine, 6-mercaptopurine, and methotrexate. An exception to the requirement for a trial of or contraindication to steroids or a trial of one other conventional systemic agent can be made if the patient has already tried at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for Crohn's disease. A trial of mesalamine does not count as a systemic agent for Crohn's disease.
       - **c)** Patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas; OR

d) Patient had ileocolonic resection (to reduce the chance of Crohn's disease recurrence); AND

iii. The medication is prescribed by or in consultation with a gastroenterologist.

D) Patient is Currently Receiving Cimzia. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

iii. Patient meets at least one of the following (a or b):

c) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR

E) Note: Examples of objective measures include fecal markers (e.g., fecal lactoferrin, fecal calprotectin), serum markers (e.g., C-reactive protein), imaging studies (magnetic resonance enterography [MRE], computed tomography enterography [CTE]), endoscopic assessment, and/or reduced dose of corticosteroids.

d) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or blood in stool.

3. Non-Radiographic Axial Spondyloarthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient has objective signs of inflammation, defined as at least one of the following (a or b):

a) C-reactive protein (CRP) elevated beyond the upper limit of normal for the reporting laboratory; OR

b) Sacroiliitis reported on magnetic resonance imaging (MRI); AND

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Cimzia. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on the requested drug for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondylarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

4. Plaque Psoriasis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets ONE of the following conditions (a or b):

a) Patient has tried at least at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR

Note: Examples of traditional systemic agents for psoriasis include methotrexate, cyclosporine, acitretin tablets, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already had a 3-month trial or previous intolerance to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for psoriasis. A patient who has already tried a biologic for psoriasis is not required to "step back" and try a traditional systemic agent for psoriasis.

b) Patient has a contraindication to methotrexate, as determined by the prescriber; AND

iii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Cimzia. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has been established on the requested drug for at least 90 days; AND

F) Note: A patient who has received < 90 days of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).

ii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating the requested drug) in at least one of the following: estimated body surface area affected by psoriasis, erythema, induration/thickness, and/or scale of areas affected by psoriasis; AND

iii. Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain, itching, and/or burning.

G)

5. Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving Cimzia. Approve for 1 year if the patient meets BOTH of the following (i and ii):

iii. Patient has been established on the requested drug for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).

iv. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR

Note: Examples of standardized measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsA DAS), Grace Index, Leeds Enthesitis Score (LEI), Spondyloarthritis Consortuium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths).

ii.

6. Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i and ii):

i. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND

Note: Examples of conventional synthetic DMARDs include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already had a 3-month trial of at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for rheumatoid arthritis. A patient who has already tried a biologic for rheumatoid arthritis is not required to "step back" and try a conventional synthetic DMARD.

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Cimzia. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on the requested drug for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR

Note: Examples of standardized and validated measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).

b) Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

Other Uses with Supportive Evidence

7. Spondyloarthritis, Other Subtypes. Approve for the duration noted if the patient meets ONE of the following conditions (A or B):

Note: Examples of other subtypes of spondyloarthritis include undifferentiated arthritis and reactive arthritis (Reiter's disease). For ankylosing spondylitis, psoriatic arthritis, or non-radiographic axial spondyloarthritis, refer to the respective criteria under FDA-approved indications.

C) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient has arthritis primarily in the knees, ankles, elbows, wrists, hands, and/or feet; AND

ii. Patient has tried at least ONE conventional synthetic disease-modifying antirheumatic drug (DMARD); AND

H) No

te: Examples include methotrexate, leflunomide, and sulfasalazine.

iii. The medication is prescribed by or in consultation with a rheumatologist.

D) Patient is Currently Receiving Cimzia. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on the requested drug for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).

ii. Patients meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR

Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS) and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cimzia is not recommended in the following situations:

4. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Cimzia should not be administered in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see Appendix for examples). Combination therapy is generally not recommended due to a potentially higher rate of AEs with combinations and lack of data supportive of additional efficacy. Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Cimzia.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

[*] Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARDs – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Cosentyx Intravenous Prior Authorization Policy
- Cosentyx® (secukinumab intravenous infusion – Novartis)

REVIEW DATE: 11/01/2023

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179. OVERVIEW

180. Cosentyx intravenous, an interleukin (IL)-17A antagonist, is indicated in the following conditions:[1]

- **Psoriatic arthritis**, in adults with active disease.
- **Ankylosing spondylitis**, in adults with active disease.
- **Non-radiographic axial spondyloarthritis**, in adults with active disease and objective signs of inflammation.

181.

182. In the pivotal trial for non-radiographic axial spondyloarthritis, patients were required to have objective signs of inflammation, indicated by elevated C-reactive protein and/or sacroiliitis on magnetic resonance imaging.

183.

Dosing Information

8. For approved uses, Cosentyx intravenous may be given with or without a single 6 mg/kg loading dose. The maintenance dose is 1.75 mg/kg given intravenously once every 4 weeks.

184.

185. Guidelines

186. The intravenous formulation of Cosentyx has not been addressed in any guidelines. However, Il-17 blockers, including the subcutaneous formulation of Cosentyx, are mentioned in guidelines for treatment of inflammatory conditions.

- **Ankylosing Spondylitis and Non-Radiographic Axial Apondyloarthritis:** Guidelines for ankylosing spondylitis and non-radiographic axial spondyloarthritis are published by the ACR/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019).[2] Following primary nonresponse to a TNFi, either Cosentyx or Taltz® (ixekizumab injection) is recommended; however, if the patient is a secondary nonresponder, a second TNFi is recommended over switching out of the class. In patients with a contraindication to a TNFi, use of an IL-17 blocker is recommended over traditional oral agents such as methotrexate or sulfasalazine.
- **Psoriatic Arthritis:** Guidelines from the American College of Rheumatology (ACR)/National Psoriasis Foundation (2018) generally recommend TNFis as the first-line treatment strategy over other biologics (e.g., IL-17 blockers) with differing mechanisms of action.[3]

187. POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cosentyx intravenous. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cosentyx intravenous as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Cosentyx intravenous to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cosentyx intravenous is recommended in those who meet one of the following criteria:

FDA-Approved Indications

PP) Ankylosing Spondylitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Cosentyx Intravenous or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **i.** Patient has been established on Cosentyx intravenous or subcutaneous for at least 6 months; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy with Cosentyx intravenous or subcutaneous is reviewed under criterion A (Initial Therapy).
- **ii.** Patient meets at least ONE of the following (a or b):
  - **1.** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Cosentyx intravenous or subcutaneous); OR
    Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondyloarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).
  - **2.** Compared with baseline (prior to initiating Cosentyx intravenous or subcutaneous), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

v.

QQ) Non-Radiographic Axial Spondyloarthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has objective signs of inflammation, defined as at least ONE of the following (a or b):
  - **a)** C-reactive protein elevated beyond the upper limit of normal for the reporting laboratory; OR
  - **b)** Sacroiliitis reported on magnetic resonance imaging; AND
- **iii.** The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Cosentyx Intravenous or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **iii.** Patient has been established on Cosentyx intravenous or subcutaneous for at least 6 months; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy with Cosentyx intravenous or subcutaneous is reviewed under criterion A (Initial Therapy).
- **iv.** Patient meets at least ONE of the following (a or b):
  - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Cosentyx intravenous or subcutaneous); OR
    Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional

Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondyloarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating Cosentyx intravenous or subcutaneous), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

RR) Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets both of the following (i and ii):

i. Patient is ≥ 18 years of age; AND

ii. The medication is prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving Cosentyx Intravenous or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

vi. Patient has been established on Cosentyx intravenous or subcutaneous for at least 6 months; AND

Note: A patient who has received < 6 months of therapy with Cosentyx intravenous or subcutaneous or who is restarting therapy is reviewed under criterion A (Initial Therapy).

vii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Cosentyx intravenous or subcutaneous); OR

9. Note: Examples of standardized measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsA DAS), Grace Index, Leeds Enthesitis Score (LEI), Spondyloarthritis Consortium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating Cosentyx intravenous or subcutaneous), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cosentyx intravenous is not recommended in the following situations:

1. **Concurrent Use with other Biologics or Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs).** Cosentyx intravenous should not be administered in combination with another biologic or targeted synthetic DMARD used for an inflammatory condition (See Appendix for examples). Combination therapy is generally not recommended due to the potential for a higher rate of adverse effects with combination therapies and lack of evidence for additive efficacy.

10. Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Cosentyx intravenous.

188. Crohn's Disease. Exacerbations of Crohn's disease, in some cases serious, occurred in clinical trials in patients treated with Cosentyx.[1] In a Phase II published study in patients with Crohn's disease (n = 59), an intravenous formulation of Cosentyx did not reduce the Crohn's disease activity index by ≥ 50 points compared with placebo and the study was terminated prematurely.[4]

11.

189. Enthesitis-Related Arthritis. Cosentyx subcutaneous is indicated and has approved dosing regimens for treatment of enthesitis-related arthritis.[1]

12.

190. Plaque Psoriasis. Cosentyx subcutaneous is indicated and has approved dosing regimens for treatment of plaque psoriasis.[1]

191. Rheumatoid Arthritis. In a published, double-dummy Phase III study, Cosentyx was less effective than current treatments in patients with rheumatoid arthritis who were previously treated with a tumor necrosis factor inhibitor (TNFi).[5] Patients were randomized to one of four treatment groups: 1) induction with an intravenous formulation of Cosentyx (10 mg/kg) followed by Cosentyx 150 mg subcutaneously given once every 4 weeks (Q4W) [n = 137]; 2) secukinumab intravenous induction (10 mg/kg) followed by Cosentyx 75 mg subcutaneously Q4W (n = 138). At Week 24, ACR 20 response was significantly better with Cosentyx 150 mg subcutaneous (31%) and Orencia intravenous (43%) vs. placebo (18%). ACR 20 response with Cosentyx 75 mg was 28%, which was not significantly better than the placebo group. ACR 50/70 responses were 17%/10% with Cosentyx 150 mg and 12%/5% with Cosentyx 75 mg which was not significantly different from that of placebo (9%/5%). The group treated with Orencia intravenous had significantly improved ACR 50/70 responses at Week 24 (28%/12%). Using as observed data, ACR 20/50/70 responses at Week 52 were 63%/46%/19% with Cosentyx 150 mg, 57%/26%/7% with Cosentyx 75 mg, and 75%/52%/23% with Orencia intravenous. There is a published Phase II dose-ranging study (n = 237) evaluating Cosentyx in rheumatoid arthritis.[6-8] The ACR 20 response at Week 16 (using last observation carried forward analysis) was 34%, 46.9%, 46.5%, 53.7% for the 25, 75, 150, and 300 mg doses vs. 36% for placebo; however, this did not achieve statistical significance. After Week 16, patients who responded to Cosentyx had sustained response through Week 52, with patients on the 150 mg dose having the greatest improvement over time (55% and 40% of patients with ACR 50 and ACR 70 responses, respectively, at Week 52). In another Phase II study, Cosentyx did not achieve higher ACR 20 response rates at Week 12 vs. placebo.[9] There was an open-label treatment period where ACR responses were generally maintained through Week 52. Some patients were treated with an intravenous formulation of secukinumab and generally responded similarly to those treated with Cosentyx subcutaneous. In another Phase II study, an intravenous formulation of secukinumab demonstrated limited efficacy in biologic-naïve patients with rheumatoid arthritis associated with the HLA-DRB1 allele.[10]

192. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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193.
194.

APPENDIX

[*] Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; PMR – Polymyalgia rheumatic; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Cosentyx Subcutaneous Prior Authorization Policy
- Cosentyx® (secukinumab subcutaneous injection – Novartis)

REVIEW DATE: 11/01/2023; selected revision 11/15/2023

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v. OVERVIEW

vi. Cosentyx subcutaneous, an interleukin (IL)-17A antagonist, is indicated in the following conditions:[1]

- **Enthesitis-related arthritis**, in patients ≥ 4 years of age with active disease.
- **Hidradenitis suppurativa**, in adults with moderate to severe disease.
- **Plaque psoriasis**, in patients ≥ 6 years of age with moderate to severe disease who are candidates for systemic therapy or phototherapy.
- **Psoriatic arthritis**, in patients ≥ 2 years of age with active disease.
- **Ankylosing spondylitis**, in adults with active disease.
- **Non-radiographic axial spondyloarthritis**, in adults with active disease and objective signs of inflammation.

vii.

viii. In the pivotal trial for non-radiographic axial spondyloarthritis, patients were required to have objective signs of inflammation, indicated by elevated C-reactive protein and/or sacroiliitis on magnetic resonance imaging.

ix.

x. Guidelines

xi. Il-17 blockers are mentioned in multiple guidelines for treatment of inflammatory conditions.

- **Enthesitis-Related Arthritis:** Guidelines for juvenile idiopathic arthritis from the American College of Rheumatology (ACR) [2018] address treatment of enthesitis-related arthritis.[14] These recommendations were developed prior to approval of Cosentyx. A tumor necrosis factor inhibitor (TNFi) is recommended over use of methotrexate or sulfasalazine in those who have tried a nonsteroidal anti-inflammatory drug (NSAID).
- **Plaque Psoriasis:** Joint guidelines of care for the management and treatment of psoriasis with biologics were published by the American Academy of Dermatology (AAD) and the National Psoriasis Foundation (2019).[3] All of the biologics are generally recommended for treatment of moderate to severe disease. The AAD also recommends methotrexate (unless contraindicated) and other systemic therapies for treatment of moderate to severe psoriasis.[4] Traditional systemic agents can benefit widespread psoriasis. Studies have assessed response to methotrexate following 6 weeks to 4 months of treatment.
- **Psoriatic Arthritis:** Guidelines from ACR/National Psoriasis Foundation (2018) generally recommend TNFis as the first-line treatment strategy over other biologics (e.g., IL-17 blockers) with differing mechanisms of action.[5]
- **Ankylosing Spondylitis and Non-Radiographic Axial Apondyloarthritis:** Guidelines for ankylosing spondylitis and non-radiographic axial spondyloarthritis are published by the ACR/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019).[2] Following primary nonresponse to a TNFi, either Cosentyx or Taltz® (ixekizumab injection) is recommended; however, if the patient is a secondary nonresponder, a second TNFi is recommended over switching out of the class. In patients with a contraindication to a TNFi, use of an IL-17 blocker is recommended over traditional oral agents such as methotrexate or sulfasalazine.

xii. POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cosentyx subcutaneous. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cosentyx subcutaneous as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Cosentyx subcutaneous to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cosentyx subcutaneous is recommended in those who meet the following criteria:

FDA-Approved Indications

SS) Ankylosing Spondylitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

- **A)** Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist.
- **B)** Patient is Currently Receiving Cosentyx Subcutaneous or Intravenous. Approve for 1 year if the patient meets BOTH of the following (i and ii):
  - **i.** Patient has been established on Cosentyx subcutaneous or intravenous for at least 6 months; AND
    Note: A patient who has received < 6 months of therapy or who is restarting therapy with Cosentyx subcutaneous or intravenous is reviewed under criterion A (Initial Therapy).
  - **ii.** Patient meets at least ONE of the following (a or b):
    - **1.** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Cosentyx subcutaneous or intravenous); OR
      Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondyloarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).
    - **2.** Compared with baseline (prior to initiating Cosentyx subcutaneous or intravenous), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

TT) Enthesitis-Related Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

- **A)** Initial Therapy. Approve for 6 months if the patient meets both of the following (i and ii):
  - **i.** Patient is ≥ 4 years of age; AND
  - **ii.** The medication is prescribed by or in consultation with a rheumatologist.
- **B)** Patient is Currently Receiving Cosentyx Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):
  - **i.** Patient has been established on Cosentyx subcutaneous for at least 6 months; AND
    Note: A patient who has received < 6 months of therapy or who is restarting therapy with Cosentyx subcutaneous is reviewed under criterion A (Initial Therapy).
  - **ii.** Patient meets at least one of the following (a or b):

d) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Cosentyx subcutaneous); OR
Note: Examples of objective measures include the Juvenile Arthritis Disease Activity Score (JADAS); Physician Global Assessment (MD global), Parent/Patient Global Assessment of Overall Well-Being (PGA), Parent/Patient Global Assessment of Disease Activity (PDA), Juvenile Arthritis Disease Activity Score (JDAS), Clinical Juvenile Arthritis Disease Activity Score (cJDAS), Juvenile Spondyloarthritis Disease Activity Index (JSpADA), serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

e) Compared with baseline (prior to initiating Cosentyx subcutaneous), patient experienced an improvement in at least one symptom, such as improvement in limitation of motion, less joint pain or tenderness, decreased duration of morning stiffness or fatigue, improved function or activities of daily living.

UU) Hidradenitis Suppurativa. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient has tried at least one other therapy; AND
Note: Examples include intralesional or oral corticosteroids (e.g., triamcinolone, prednisone), systemic antibiotics (e.g., clindamycin, dicloxacillin, erythromycin), and isotretinoin.

iii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Cosentyx Subcutaneous. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

iv. Patient has been established on therapy for at least 90 days; AND
ii. Note: A patient who has received < 90 days of therapy or who is restarting therapy with Cosentyx subcutaneous is reviewed under criterion A (Initial Therapy).

v. When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Cosentyx subcutaneous); AND
iii. Note: Examples of objective measures include Hurley staging, Sartorius score, Physician Global Assessment, and Hidradenitis Suppurativa Severity Index.

vi. Compared with baseline (prior to initiating Cosentyx subcutaneous), patient experienced an improvement in at least one symptom, such as decreased pain or drainage of lesions, nodules, or cysts.

VV) Non-Radiographic Axial Spondyloarthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient has objective signs of inflammation, defined as at least ONE of the following (a or b):

a) C-reactive protein elevated beyond the upper limit of normal for the reporting laboratory; OR

b) Sacroiliitis reported on magnetic resonance imaging; AND

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Cosentyx Subcutaneous or Intravenous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

xiii. Patient has been established on Cosentyx subcutaneous or intravenous for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with Cosentyx subcutaneous or intravenous is reviewed under criterion A (Initial Therapy).

xiv. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Cosentyx subcutaneous or intravenous); OR
Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondyloarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating Cosentyx subcutaneous or intravenous), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

WW) Plaque Psoriasis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following criteria (i, ii, and iii):

i. Patient is ≥ 6 years of age; AND

ii. Patient meets ONE of the following conditions (a or b):

1. Patient has tried at least at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR
Note: Examples include methotrexate, cyclosporine, acitretin, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already had a 3-month trial or previous intolerance to at least one biologic other than Cosentyx. A biosimilar of Cosentyx does not count. Refer to **Appendix** for examples of biologics used for psoriasis. A patient who has already tried a biologic for psoriasis is not required to "step back" and try a traditional systemic agent for psoriasis.

2. Patient has a contraindication to methotrexate, as determined by the prescriber; AND

iii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Cosentyx Subcutaneous. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has been established on Cosentyx subcutaneous for at least 90 days; AND
Note: A patient who has received < 90 days of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating Cosentyx subcutaneous) in at least one of the following: estimated body surface area, erythema, induration/thickness, and/or scale of areas affected by psoriasis; AND

iii. Compared with baseline (prior to initiating Cosentyx subcutaneous), patient experienced an improvement in at least one symptom, such as decreased pain, itching, and/or burning.

XX) Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets both of the following (i and ii):

i. Patient is ≥ 2 years of age; AND

ii. The medication is prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving Cosentyx Subcutaneous or Intravenous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

viii. Patient has been established on Cosentyx subcutaneous or intravenous for at least 6 months; AND

Note: A patient who has received < 6 months of therapy with Cosentyx subcutaneous or intravenous or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ix. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Cosentyx subcutaneous or intravenous); OR

iv. Note: Examples of standardized measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsA DAS), Grace Index, Leeds Enthesitis Score (LEI), Spondyloarthritis Consortium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating Cosentyx subcutaneous or intravenous), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cosentyx subcutaneous is not recommended in the following situations:

1. **Concurrent Use with other Biologics or Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs).** Cosentyx should not be administered in combination with another biologic or targeted synthetic DMARD used for an inflammatory condition (See Appendix for examples). Combination therapy is generally not recommended due to the potential for a higher rate of adverse effects with combination therapies and lack of evidence for additive efficacy.
   Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Cosentyx.

101. Crohn's Disease. Exacerbations of Crohn's disease, in some cases serious, occurred in clinical trials in patients treated with Cosentyx.[1] In a Phase II published study in patients with Crohn's disease (n = 59), an intravenous formulation of Cosentyx did not reduce the Crohn's disease activity index by ≥ 50 points compared with placebo and the study was terminated prematurely.[6]

v.

102. Rheumatoid Arthritis. In a published, double-dummy Phase III study, Cosentyx was less effective than current treatments in patients with rheumatoid arthritis who were previously treated with a tumor necrosis factor inhibitor (TNFi).[7] Patients were randomized to one of four treatment groups: 1) induction with an intravenous formulation of Cosentyx (10 mg/kg) followed by Cosentyx 150 mg subcutaneously given once every 4 weeks (Q4W) [n = 137]; 2) secukinumab intravenous induction (10 mg/kg) followed by Cosentyx 75 mg subcutaneously Q4W (n = 138). At Week 24, ACR 20 response was significantly better with Cosentyx 150 mg subcutaneous (31%) and Orencia (abatacept intravenous [IV] injection) [43%] vs. placebo (18%). ACR 20 response with Cosentyx 75 mg was 28%, which was not significantly better than the placebo group. ACR 50/70 responses were 17%/10%, respectively, with Cosentyx 150 mg and 12%/5%, respectively, with Cosentyx 75 mg which were not significantly different from that of placebo (9%/5%, respectively). The group treated with Orencia intravenous had significantly improved ACR 50/70 responses at Week 24 (28%/12%). Using as observed data, ACR 20/50/70 responses at Week 52 were 63%/46%/19%, respectively, with Cosentyx 150 mg, 57%/26%/7%, respectively, with Cosentyx 75 mg, and 75%/52%/23%, respectively, with Orencia intravenous. There is a published Phase II dose-ranging study (n = 237) evaluating Cosentyx in rheumatoid arthritis.[8-10] The ACR 20 response at Week 16 (using last observation carried forward

analysis) was 34%, 46.9%, 46.5%, 53.7% for the 25, 75, 150, and 300 mg doses, respectively, vs. 36% for placebo; however, this did not achieve statistical significance. After Week 16, patients who responded to Cosentyx had sustained response through Week 52, with patients on the 150 mg dose having the greatest improvement over time (55% and 40% of patients with ACR 50 and ACR 70 responses, respectively, at Week 52). In another Phase II study, Cosentyx did not achieve higher ACR 20 response rates at Week 12 vs. placebo.[11] There was an open-label treatment period where ACR responses were generally maintained through Week 52. Some patients were treated with an intravenous formulation of secukinumab and generally responded similarly to those treated with Cosentyx. In another Phase II study, an intravenous formulation of secukinumab demonstrated limited efficacy in biologic-naïve patients with rheumatoid arthritis associated with the HLA-DRB1 allele.[12]

vi.

103. Uveitis. Efficacy is not established for this condition. There was not a statistically significant difference between Cosentyx subcutaneous and placebo in three Phase III studies that included patients with Behcet's uveitis (n = 118); active, noninfectious, non-Behcet's uveitis (n = 31); and quiescent, noninfectious, non-Behcet's uveitis (n = 125) [SHEILD, INSURE, and ENDURE studies, respectively].[13]

104. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

xv. REFERENCES

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13.

14.
xvi.

xvii. APPENDIX

* Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; PMR – Polymyalgia rheumatic; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Entyvio Intravenous Prior Authorization Policy
- Entyvio® (vedolizumab intravenous infusion – Takeda)

REVIEW DATE: 10/11/2023

OVERVIEW

Entyvio intravenous (IV), an integrin receptor antagonist, is indicated for the following uses:[1]
- **Crohn's disease**, in adults with moderately to severely active disease.
- **Ulcerative colitis**, in adults with moderately to severely active disease.

Therapy begins with Entyvio 300 mg IV at Week 0 and Week 2. At Week 6, or at any scheduled Entyvio IV infusion in patients with a clinical response or remission, therapy can be switched to Entyvio SC. The recommended dose of Entyvio SC is 108 mg SC once every 2 weeks. In the pivotal studies evaluating Entyvio, all patients had previously tried corticosteroids and/or conventional agents for Crohn's disease and ulcerative colitis.

Guidelines

Guidelines for the treatment of inflammatory conditions recommend use of Entyvio.
- **Crohn's Disease:** The American College of Gastroenterology (ACG) has updated guidelines (2018) for Crohn's disease.[2] Entyvio is among the recommendations for treatment of patients with moderate to severe disease or moderate to high risk disease (for induction of remission as well as maintenance of this remission). Guidelines from the American Gastroenterological Association (AGA) [2021] include Entyvio among the therapies for moderate to severe Crohn's disease, for induction and maintenance of remission.[5]
- **Ulcerative Colitis:** Updated ACG guidelines for ulcerative colitis (2019) note that the following agents can be used for induction of remission in moderately to severely active disease: Uceris® (budesonide extended-release tablets); oral or intravenous systemic corticosteroids, Entyvio, Xeljanz® (tofacitinib tablets), or tumor necrosis factor inhibitors.[3] Current guidelines for ulcerative colitis from the AGA (2020) include Entyvio among the therapies recommended for moderate to severe disease.[6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Entyvio intravenous. All approvals are provided for the duration listed below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Entyvio intravenous as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Entyvio intravenous to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Entyvio intravenous is recommended in those who meet one of the following:

FDA-Approved Indications

1. **Crohn's Disease.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient meets ONE of the following (a, b, c, or d):
       - **a)** Patient has tried or is currently taking systemic corticosteroids, or corticosteroids are contraindicated in this patient; OR
       - **b)** Patient has tried one conventional systemic therapy for Crohn's disease; OR
         Note: Examples of conventional systemic therapy for Crohn's disease include azathioprine, 6-mercaptopurine, or methotrexate. An exception to the requirement for a trial of or contraindication to steroids or a trial of one other conventional systemic agent can be made if the patient has already tried at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for Crohn's disease. These patients who have already received a biologic are not required to "step back" and try another agent. A trial of mesalamine does not count as a systemic therapy for Crohn's disease.
       - **c)** Patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas; OR
       - **d)** Patient had ileocolonic resection (to reduce the chance of Crohn's disease recurrence); AND
     - **iii.** The medication is prescribed by or in consultation with a gastroenterologist.
   - **B)** Patient is Currently Receiving Entyvio. Approve for 1 year if the patient meets BOTH of the following (i and ii):
     - **i.** Patient has been established on the requested drug for at least 6 months; AND
       Note: A patient who has received < 6 months of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).
     - **ii.** Patient meets at least one of the following (a or b):
       - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
         a) Note: Examples of objective measures include fecal markers (e.g., fecal lactoferrin, fecal calprotectin), serum markers (e.g., C-reactive protein), imaging studies (magnetic resonance enterography [MRE], computed tomography enterography [CTE]), endoscopic assessment, and/or reduced dose of corticosteroids.
       - **b)** Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or blood in stool.

2. **Ulcerative Colitis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient meets ONE of the following (a or b):
       - **a)** Patient has had a trial of ONE systemic therapy; OR
         b) Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone or methylprednisolone. A trial of a mesalamine product does not count as a systemic therapy for ulcerative colitis. A trial of a biologic also counts as a trial of one systemic agent for ulcerative colitis. Refer to Appendix for examples of biologics used for ulcerative colitis.
       - **b)** Patient meets BOTH of the following [(1) and (2)]:
         - **(1)** Patient has pouchitis; AND
         - **(2)** Patient has tried an antibiotic, probiotic, corticosteroid enema, or mesalamine enema; AND

c) Note: Examples of antibiotics include metronidazole and ciprofloxacin. Examples of corticosteroid enemas include hydrocortisone enema.

iii. The medication is prescribed by or in consultation with a gastroenterologist.

B) Patient is Currently Receiving Entyvio (Intravenous or Subcutaneous). Approve for 1 year if the patient meets BOTH of the following (i and ii):

ii. Patient has been established on Entyvio intravenous or subcutaneous for at least 6 months; AND

d) Note: A patient who has received < 6 months of therapy or who is restarting therapy with Entyvio intravenous or subcutaneous is reviewed under criterion A (Initial Therapy).

iii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR

e) Note: Examples of assessment for inflammatory response include fecal markers (e.g., fecal calprotectin), serum markers (e.g., C-reactive protein), endoscopic assessment, and/or reduced dose of corticosteroids.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or decreased rectal bleeding.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Entyvio intravenous is not recommended in the following situations:

1. **Concurrent Use with Other Biologics or with Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs) used for an Inflammatory Condition.** Entyvio should not be used in combination with tumor necrosis factor inhibitors or with Tysabri due to increased risk of infections.[1] There is also an increased risk of progressive multifocal leukoencephalopathy if used in combination with Tysabri. Combination therapy with other biologics or with targeted synthetic DMARDs used to treat inflammatory conditions (see Appendix for examples) is generally not recommended due to a potential for a higher rate of adverse effects with combinations and lack of data supportive of additive efficacy.
   Note: This does NOT exclude the use of conventional immunosuppressants (e.g., 6-mercaptopurine, azathioprine) in combination with Entyvio.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterology*. 2020;158(5):1450-1461.

APPENDIX

[*] Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Entyvio Subcutaneous Prior Authorization Policy
- Entyvio® (vedolizumab subcutaneous injection – Takeda)

REVIEW DATE: 10/11/2023

OVERVIEW

Entyvio subcutaneous, an integrin receptor antagonist, is indicated for treatment of **ulcerative colitis**, in adults with moderate to severe active disease who have received two induction doses with Entyvio intravenous.[1]

Therapy begins with Entyvio 300 mg IV at Week 0 and Week 2. At Week 6, or at any scheduled Entyvio IV infusion in patients with a clinical response or remission, therapy can be switched to Entyvio SC. The recommended dose of Entyvio SC is 108 mg SC once every 2 weeks. In the pivotal studies evaluating Entyvio subcutaneous, all patients had previously tried corticosteroids, conventional agents, or biologics for ulcerative colitis.

Guidelines

Guidelines for the treatment of inflammatory conditions recommend use of Entyvio.

- **Ulcerative Colitis:** Updated American College of Gastroenterology guidelines for ulcerative colitis (2019) note that the following agents can be used for induction of remission in moderately to severely active disease: Uceris® (budesonide extended-release tablets); oral or intravenous systemic corticosteroids, Entyvio, Xeljanz® (tofacitinib tablets), or tumor necrosis factor inhibitors.[2] Current guidelines for ulcerative colitis from the American Gastroenterological Association (2020) include Entyvio among the therapies recommended for moderate to severe disease.[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Entyvio subcutaneous. All approvals are provided for the duration listed below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Entyvio subcutaneous as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Entyvio subcutaneous to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Entyvio subcutaneous is recommended in those who meet one of the following:

FDA-Approved Indications

1. **Ulcerative Colitis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

i. According to the prescriber, the patient is currently receiving Entyvio intravenous or will receive induction dosing with Entyvio intravenous within 2 months of initiating therapy with Entyvio subcutaneous; AND

ii. Patient meets ONE of the following (a or b):

c) Patient has had a trial of ONE systemic therapy; OR

283. Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone or methylprednisolone. A trial of a mesalamine product does not count as a systemic therapy for ulcerative colitis. A trial of a biologic also counts as a trial of one systemic agent for ulcerative colitis. Refer to Appendix for examples of biologics used for ulcerative colitis.

d) Patient meets BOTH of the following [(1) and (2)]:

(1) Patient has pouchitis; AND

(2) Patient has tried an antibiotic, probiotic, corticosteroid enema, or mesalamine enema; AND

284. Note: Examples of antibiotics include metronidazole and ciprofloxacin. Examples of corticosteroid enemas include hydrocortisone enema.

iii. The medication is prescribed by or in consultation with a gastroenterologist.

B) Patient is Currently Receiving Entyvio (Subcutaneous or Intravenous). Approve for 1 year if the patient meets BOTH of the following (i and ii):

iv. Patient has been established on Entyvio subcutaneous or intravenous for at least 6 months; AND

285. Note: A patient who has received < 6 months of therapy or who is restarting therapy with Entyvio subcutaneous or intravenous is reviewed under criterion A (Initial Therapy).

v. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR

286. Note: Examples of assessment for inflammatory response include fecal markers (e.g., fecal calprotectin), serum markers (e.g., C-reactive protein), endoscopic assessment, and/or reduced dose of corticosteroids.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or decreased rectal bleeding.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Entyvio subcutaneous is not recommended in the following situations:

1. **Concurrent Use with Other Biologics or with Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs) used for an Inflammatory Condition.** Entyvio should not be used in combination with tumor necrosis factor inhibitors or with Tysabri due to increased risk of infections.[1] There is also an increased risk of progressive multifocal leukoencephalopathy if used in combination with Tysabri. Combination therapy with other biologics or with targeted synthetic DMARDs used to treat inflammatory conditions (see Appendix for examples) is generally not recommended due to a potential for a higher rate of adverse effects with combinations and lack of data supportive of additive efficacy.

   Note: This does NOT exclude the use of conventional immunosuppressants (e.g., 6-mercaptopurine, azathioprine) in combination with Entyvio.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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290. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterology*. 2020;158(5):1450-1461.

APPENDIX

[*] Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Etanercept Products Prior Authorization Policy
- Enbrel® (etanercept subcutaneous injection – Immunex/Amgen)

REVIEW DATE: 10/18/2023

OVERVIEW

Etanercept products are tumor necrosis factor inhibitors (TNFis) approved for the following uses:[1]

- **Ankylosing spondylitis**, for reducing signs and symptoms in patients with active disease.
- **Juvenile idiopathic arthritis (JIA)**, for reducing the signs and symptoms of moderate or severe active polyarticular disease in patients ≥ 2 years of age.
- **Plaque psoriasis**, for treatment patients ≥ 4 years of age with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
- **Psoriatic arthritis**, ± methotrexate for reducing the signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function.
- **Rheumatoid arthritis**, ± methotrexate for reducing the signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderate or severe active disease.

x.

Guidelines

TNFis feature prominently in guidelines for treatment of inflammatory conditions.

- **Ankylosing Spondylitis and Spondyloarthritis:** Guidelines for ankylosing spondylitis and non-radiographic axial spondylitis are published by the American College of Rheumatology (ACR)/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019).[5] TNFis are recommended for the initial biologic. In those who are secondary non-responders to a TNFi, a second TNFi is recommended over switching out of the class.
- **JIA:** There are guidelines from ACR and the Arthritis Foundation for the treatment of JIA (2021) which address oligoarthritis and temporomandibular joint (TMJ) arthritis.[47] For oligoarthritis, a biologic is recommended following a trial of a conventional synthetic disease-modifying antirheumatic drug (DMARD). In patients with TMJ arthritis, scheduled nonsteroidal anti-inflammatory drugs (NSAIDs) and/or intra-articular glucocorticoids are recommended first-line. A biologic is a therapeutic option if there is an inadequate response or intolerance. Additionally, rapid escalation to a biologic ± conventional synthetic DMARD (methotrexate preferred) is often appropriate given the impact and destructive nature of TMJ arthritis. In these guidelines, there is not a preferred biologic that should be initiated for JIA. There are also guidelines from the ACR/Arthritis Foundation for the treatment of JIA (2019) specific to juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis.[3] TNFis are the biologics recommended for polyarthritis, sacroiliitis, and enthesitis. Biologics are recommended following other therapies (e.g., following DMARDs for active polyarthritis or following an NSAID for active JIA with sacroiliitis or enthesitis). However, there are situations where initial therapy with a biologic may be preferred over other conventional therapies (e.g., if there is involvement of high-risk joints such as the cervical spine, wrist, or hip; high disease activity; and/or those judged to be at high risk of disabling joint damage). TNFis may also be used as second- or third-line treatment for systemic JIA.[4]
- **Plaque Psoriasis:** Guidelines from the American Academy of Dermatologists and National Psoriasis Foundation (2019) recommend etanercept as a monotherapy treatment option for adults with moderate to severe disease.[7]

- **Psoriatic Arthritis:** Guidelines from ACR (2019) recommend TNFis over other biologics for use in treatment-naïve patients with psoriatic arthritis and in those who were previously treated with an oral therapy.[8]
- **Rheumatoid Arthritis:** Guidelines from ACR (2021) recommend addition of a biologic or a targeted synthetic DMARD for a patient taking the maximum tolerated dose of methotrexate who is not at target.[22]

xi.

Other Uses with Supportive Evidence

There are guidelines and/or published data supporting the use of etanercept products in the following conditions:

- **Behcet's Disease:** The European Union Against Rheumatism (EULAR) recommendations (2018) include TNFis for initial or recurrent sight-threatening uveitis.[9] For patients refractory to first-line treatments (e.g., corticosteroids), TNFis are among the treatment options for mucocutaneous manifestations, venous thrombosis, severe or refractory gastrointestinal disease, and recurrent/chronic joint involvement. Recommendations for the use of TNFis in ocular inflammatory disorders from the American Academy of Ophthalmology (AAO) [2014] note that TNFis may be used first-line in patients with ophthalmic manifestations of Behcet's disease and for acute exacerbations of pre-existing Behcet's disease.[8] In particular, the monoclonal antibodies (adalimumab or infliximab products) are recommended for vision-threatening ocular manifestations of Behcet's disease.
- **Graft-Versus-Host Disease:** Guidelines for hematopoietic cell transplantation from the National Comprehensive Cancer Network (version 2.2022 – September 28, 2022) list etanercept among the agents used for steroid-refractory acute and chronic disease.[46]
- **Pyoderma Gangrenosum:** Although guidelines are not current, multiple topical and systemic therapies have been used for pyoderma gangrenosum. Oral prednisone is the most common initial immunosuppressant medication.[10-13] Other systemic therapies include cyclosporine, methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, and TNFis (i.e., infliximab, etanercept, and adalimumab products). In case reports, TNFis have been effective.
- **Still's Disease:** There are not current guidelines for treatment of Still's disease. However, it presents in adults with features similar to those of systemic onset JIA.[24] In addition, there is a small trial which demonstrated efficacy of etanercept used for this condition.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of etanercept products. Because of the specialized skills required for evaluation and diagnosis of a patient as well as the monitoring required for adverse events and long-term efficacy, initial approval requires etanercept products to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of etanercept products is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Ankylosing Spondylitis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist.
   - **B)** Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):
     - **i.** Patient has been established on therapy for at least 6 months; AND
       Note: A patient who has received < 6 months of therapy or who is restarting therapy with an etanercept product is reviewed under criterion A (Initial Therapy).
     - **ii.** Patient meets at least one of the following (a or b):
       - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an etanercept product); OR
         Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondyloarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).
       - **b)** Compared with baseline (prior to initiating an etanercept product), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

2. **Juvenile Idiopathic Arthritis (JIA).** Approve for the duration noted if the patient meets ONE of the following (A or B):
   xii. Note: This includes JIA regardless of type of onset, including a patient with juvenile spondyloarthropathy/active sacroiliac arthritis. JIA is also referred to as Juvenile Rheumatoid Arthritis.
   - **A)** Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):
     - **i.** Patient meets one of the following conditions (a, b, c, or d):
       - **i)** Patient has tried one other systemic medication for this condition; OR
         xiii. Note: Examples of other systemic therapy for JIA include methotrexate, sulfasalazine, leflunomide, or a nonsteroidal anti-inflammatory drug (NSAID) [e.g., ibuprofen, naproxen]. A previous trial of one biologic other than the requested drug also counts as a trial of one agent for JIA. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for JIA.
       - **j)** Patient will be starting on therapy concurrently with methotrexate, sulfasalazine, or leflunomide; OR
       - **k)** Patient has an absolute contraindication to methotrexate, sulfasalazine, or leflunomide; OR
         xiv. Note: Examples of contraindications to methotrexate include pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, blood dyscrasias.
       - **l)** Patient has aggressive disease, as determined by the prescriber; AND
     - **ii.** The medication is prescribed by or in consultation with a rheumatologist.
   - **B)** Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):
     - **i.** Patient has been established on therapy for at least 6 months; AND
       Note: A patient who has received < 6 months of therapy or who is restarting therapy with an etanercept product is reviewed under criterion A (Initial Therapy).
     - **ii.** Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an etanercept product); OR
Note: Examples of objective measures include Physician Global Assessment (MD global), Parent/Patient Global Assessment of Overall Well-Being (PGA), Parent/Patient Global Assessment of Disease Activity (PDA), Juvenile Arthritis Disease Activity Score (JDAS), Clinical Juvenile Arthritis Disease Activity Score (cJDAS), Juvenile Spondyloarthritis Disease Activity Index (JSpADA), serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating an etanercept product), patient experienced an improvement in at least one symptom, such as improvement in limitation of motion, less joint pain or tenderness, decreased duration of morning stiffness or fatigue, improved function or activities of daily living.

xv.

3. Plaque Psoriasis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 4 years of age; AND

ii. Patient meets one of the following conditions (a or b):

a) Patient has tried at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR
Note: Examples include methotrexate, cyclosporine, acitretin, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already has a 3-month trial or previous intolerance to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. . Refer to Appendix for examples of biologics used for psoriasis. A patient who has already tried a biologic for psoriasis is not required to "step back" and try a traditional systemic agent for psoriasis.

b) Patient has a contraindication to methotrexate, as determined by the prescriber; AND

iii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has been established on therapy for at least 90 days; AND
Note: A patient who has received < 90 days of therapy or who is restarting therapy with an etanercept product is reviewed under criterion A (Initial Therapy).

ii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating an etanercept product) in at least one of the following: estimated body surface area, erythema, induration/thickness, and/or scale of areas affected by psoriasis; AND

iii. Compared with baseline (prior to receiving an etanercept product), patient experienced an improvement in at least one symptom, such as decreased pain, itching, and/or burning.

4. Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

xvi. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with an etanercept product is reviewed under criterion A (Initial Therapy).

xvii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an etanercept product); OR

C) Note: Examples of standardized measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsA DAS), Grace Index, Leeds Enthesitis Score (LEI), Spondyloarthritis Consortium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating an etanercept product), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths).

5. Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND

Note: Examples include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already has a 3-month trial at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for rheumatoid arthritis. A patient who has already tried a biologic for rheumatoid arthritis is not required to "step back" and try a conventional synthetic DMARD.

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

iv. Patient has been established on therapy for at least 6 months; AND

D) Note: A patient who has received < 6 months of therapy or who is restarting therapy with an etanercept product is reviewed under criterion A (Initial Therapy).

v. Patient meets at least one of the following (a or b):

e) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR

Note: Examples of objective measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).

E) b) Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

xviii. Other Uses with Supportive Evidence

xix.

6. Behcet's Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii):

i. Patient has tried at least one conventional therapy; AND

xx. Note: Examples include systemic corticosteroids (e.g., methylprednisolone), immunosuppressants (e.g., azathioprine, methotrexate, mycophenolate mofetil, cyclosporine,

tacrolimus, Leukeran [chlorambucil], cyclophosphamide, interferon alfa). A patient who has already tried one biologic other than the requested drug for Behcet's disease is not required to "step back" and try a conventional therapy. A biosimilar of the requested biologic does not count.

ii. The medication is prescribed by or in consultation with a rheumatologist, dermatologist, ophthalmologist, gastroenterologist, or neurologist.

B) Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has been established on therapy for at least 90 days; AND

F) Note: A patient who has received < 90 days of therapy or who is restarting therapy with an etanercept product is reviewed under criterion A (Initial Therapy).

ii. When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an etanercept product); AND

G) Note: Examples of objective measures are dependent upon organ involvement but may include best-corrected visual acuity (if ophthalmic manifestations); serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate); ulcer depth, number, and/or lesion size.

iii. Compared with baseline (prior to initiating an etanercept product), patient experienced an improvement in at least one symptom, such as decreased pain, or improved visual acuity (if ophthalmic manifestations).

xxi.

7. Graft-Versus-Host Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month if the patient meets BOTH of the following (i and ii):

i. Patient has tried at least one conventional systemic treatment for graft-versus-host disease; AND

H) Note: Examples of conventional systemic treatments include systemic corticosteroids (e.g., methylprednisolone), antithymocyte globulin, cyclosporine, tacrolimus, and mycophenolate mofetil.

ii. The medication is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center.

B) Patient is Currently Receiving an Etanercept Product. Approve for 3 months if the patient meets BOTH of the following (i and ii):

i. Patient has been established on an etanercept product for at least 1 month; AND

I) Note: A patient who has received < 1 month of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an etanercept product); OR

J) Note: Examples of objective measures are normalization of liver function tests, red blood cell count, or platelet count; or resolution of fever or rash.

b) Compared with baseline (prior to initiating an etanercept product), patient experienced an improvement in at least one symptom, such as improvement in skin, oral mucosal, ocular, or gastrointestinal symptoms (e.g., nausea, vomiting, anorexia).

xxii.

8. Pyoderma Gangrenosum. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets BOTH of the following (i and ii):

i. Patient meets ONE of the following (a or b):

a) Patient has tried one systemic corticosteroid; OR

Note: An example is prednisone.

b) Patient has tried one other immunosuppressant for at least 2 months or was intolerant to one of these medications; AND

Note: Examples include mycophenolate mofetil and cyclosporine.

ii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

iv. Patient has been established on therapy for at least 4 months; AND

K) Note: A patient who has received < 4 months of therapy or who is restarting therapy with an etanercept product is reviewed under criterion A (Initial Therapy).

v. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating an etanercept product) in at least one of the following: size, depth, and/or number of lesions; AND

vi. Compared with baseline (prior to initiating an etanercept product), patient experienced an improvement in at least one symptom, such as decreased pain and/or tenderness of affected lesion(s).

9. Spondyloarthritis, Other Subtypes. Approve for the duration noted if the patient meets ONE of the following (A or B):

L) Note: This includes undifferentiated arthritis, non-radiographic axial spondyloarthritis, Reactive Arthritis (Reiter's disease). For Ankylosing Spondylitis or Psoriatic Arthritis, refer to the respective criteria under FDA-approved indications.

E) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient meets ONE of the following conditions (a or b):

a) Patient has arthritis primarily in the knees, ankles, elbows, wrists, hands, and/or feet AND has tried at least ONE conventional synthetic disease-modifying antirheumatic drug (DMARD); OR

M) Note: Examples include methotrexate, leflunomide, sulfasalazine.

b) Patient has axial spondyloarthritis AND has objective signs of inflammation, defined as at least one of the following [(1) or (2)]:

a. C-reactive protein (CRP) elevated beyond the upper limit of normal for the reporting laboratory; OR

b. Sacroiliitis reported on magnetic resonance imaging (MRI); AND

ii. The medication is prescribed by or in consultation with a rheumatologist.

F) Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

xviii. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with an etanercept product is reviewed under criterion A (Initial Therapy).

xix. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an etanercept product); OR

Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS) and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating an etanercept product), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

10. Still's Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient has tried one corticosteroid; AND

ii. Patient has tried one conventional synthetic disease-modifying antirheumatic drug (DMARD) given for at least 2 months or was intolerant; AND

xxiii. Note: An example of a conventional synthetic DMARD is methotrexate. A previous trial of one biologic other than the requested drug (e.g., Actemra [tocilizumab intravenous injection, tocilizumab subcutaneous injection], Arcalyst [rilonacept subcutaneous injection], Ilaris [canakinumab subcutaneous injection]) also counts towards a trial of one other systemic agent for Still's disease. A biosimilar of the requested biologic does not count.

iii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

ii. Patient has been established on an this medication for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with an etanercept product is reviewed under criterion A (Initial Therapy).

iii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an etanercept product); OR
Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating an etanercept product), patient experienced an improvement in at least one symptom, such as less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of etanercept products is not recommended in the following situations:

1. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Etanercept products should not be administered in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see Appendix for examples). Combination therapy is generally not recommended due to a higher rate of adverse events (AEs) with combinations and lack of data supportive of additional efficacy.

~~**xxiv.**~~ Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with etanercept products.

xxv.

2. **Crohn's Disease.** In a double-blind, placebo-controlled trial etanercept (Enbrel) was not effective for the treatment of moderate to severe Crohn's disease.[25] However, arthritis (spondyloarthropathy, ankylosing spondylitis) may be associated with Crohn's disease and etanercept products may be effective for spondyloarthropathy in these patients.[26]

3. **Inflammatory Myopathies (Polymyositis, Dermatomyositis, Inclusion Body Myositis).** Information is conflicting. In one retrospective review of eight patients with either dermatomyositis or polymyositis some patients responded (improved motor strength and decreased fatigue) to treatment with an etanercept product.[27] In this case series, an etanercept product was added on to treatment with

corticosteroids, intravenous immunoglobulin, and DMARDs; there were no standardized outcome measures. In another case series in patients (n = 5) with dermatomyositis who had not responded to steroids and cytotoxic therapy (methotrexate, azathioprine, cyclosporine), the cytotoxic drugs were discontinued and etanercept was given for at least 3 months.[28] All patients had exacerbation of disease and etanercept was stopped. In a 1-year, double-blind study, patients were randomized to receive etanercept 50 mg weekly (n = 11) or placebo (n = 5).[29] All patients who received placebo were judged as treatment failures whereas five patients in the etanercept group were successfully weaned off of prednisone. More studies are needed demonstrating the efficacy of etanercept and its long-term effects.[30] In a 6-month, open-label study of etanercept in patients with refractory juvenile dermatomyositis (n = 9), minimal improvement was noted in disease activity with some patients experiencing worsening disease.[31]

4. **Hidradenitis Suppurativa.** A prospective, randomized, double-blind, placebo-controlled study assigned patients (n = 20) to treatment with etanercept 50 mg twice weekly or placebo for 12 weeks.[32] Following 12 weeks of treatment, all patients received open-label etanercept for an additional 12 weeks. The study found no statistically significant difference between etanercept 50 mg twice weekly and placebo among physician global assessment, patient global assessment, and the Dermatology Life Quality Index (DLQI) at Week 12 or Week 24. A systematic review (2013) extracted data from case reports and randomized, controlled trials and recommended against the use of etanercept for treatment of hidradenitis suppurativa.[33]

5. **Polymyalgia Rheumatica (PMR).** ACR/EULAR guidelines for the management of PMR (2015) strongly recommend against the use of TNFis for treatment of PMR.[34] This recommendation is based on lack of evidence for benefit as well as considerable potential for potential harm. While etanercept has been evaluated in small numbers of patients with PMR, efficacy has not been established.[35-37]

6. **Sarcoidosis.** Evidence does not support use of etanercept in ocular or pulmonary disease. Recommendations for the use of TNFis in ocular inflammatory disorders from the AAO (2014) note that infliximab or adalimumab may be considered as second-line immunomodulatory therapy for patients failing or intolerant of standard immunomodulatory agents.[8] A discretionary recommendation (indicating trade-offs are less certain) is that etanercept should not be used in the treatment of ocular sarcoidosis (moderate-quality evidence). In a double-blind study patients (n = 18) with chronic ocular sarcoidosis and ongoing inflammation were randomized to etanercept or placebo for 6 months.[38] Patients had received ≥ 6 months of therapy with methotrexate and were currently on corticosteroids. For most of the patients, therapy with etanercept was not associated with significant improvement. In a prospective, open-label trial in patients with Stage II or III progressive pulmonary sarcoidosis, treatment with etanercept was frequently associated with early or late treatment failure.[39] This trial was ended early because an excessive number of patients (n = 11/17) had disease progression on etanercept. Recommendations for best practice in the management of pulmonary and systemic sarcoidosis mention infliximab and adalimumab as therapeutic options for management of disease.[40]

xxvi.

7. **Large Vessel Vasculitis (e.g., Giant Cell Arteritis, Takayasu's Arteritis).** Guidelines from EULAR for the management of large vessel vasculitis (e.g., giant cell arteritis, Takayasu's arteritis) do not mention the use of TNFis.[41] Additionally, a meta-analysis of RCTs did not find evidence supporting remission or reduction of corticosteroid dose with the use of TNFis in large vessel vasculitis.[42] In a double-blind trial patients with biopsy proven giant cell arteritis with AEs due to corticosteroids were randomized to etanercept 25 mg twice weekly (n = 8) or placebo (n = 9) for 12 months.[43] Corticosteroids were continued but were reduced if possible according to a predefined protocol. The primary outcome was the ability to withdraw the corticosteroid therapy and control disease activity at 12 months. After 12 months, there was not a statistically significant difference in the proportion of

patients able to control disease without corticosteroid therapy with etanercept (50%) vs. placebo (22.2%). However, patients on etanercept had a significantly lower dose of accumulated prednisone during the first year of treatment (P = 0.03). In a retrospective single center study in patients with refractory Takayasu's arteritis (n = 25), patients were treated with infliximab (n = 21) or etanercept (n = 9).[44] Five patients who were initially treated with etanercept were switched to infliximab. Therapy with TNFis was associated with remission in many patients and dose reduction or discontinuation of prednisone and other immunosuppressant therapies. A randomized controlled trial is needed to better define the efficacy and safety of etanercept.

8. **Wegener's Granulomatosis.** Etanercept is not effective in the induction or maintenance of disease remissions in patients with Wegener's granulomatosis. In a double-blind trial, 180 patients with active Wegener's granulomatosis were randomized to etanercept or placebo in combination with standard therapies (e.g., cyclophosphamide, methotrexate, corticosteroids) depending on disease severity.[45] When remission was achieved, standard medications were tapered according to protocol guidelines. Patients were enrolled over 28 months and the mean follow-up was 27 months. Of the 174 patients who were evaluable, 126 patients (72.4%) achieved sustained remissions, but only 86 patients overall (49.4%) maintained their disease remissions throughout the trial. There were no differences between etanercept and the control group in the percent of patients achieving sustained remissions (69.7% vs. 75.3%, P = 0.39); in the percent of patients with sustained periods of low disease activity (86.5% vs. 90.6%); or time to achieve these outcomes. Disease flares were common in both groups. AEs were frequent and often severe. During the study, 56.2% of patients on etanercept and 57.1% on placebo had at least one severe or life-threatening adverse event or died. Six of the etanercept patients and none of the controls developed solid malignancies. Use of etanercept in patients with Wegener's granulomatosis who are receiving immunosuppressant drugs is not recommended.[1]

xxvii.

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

[*] Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Ilaris Prior Authorization Policy
- Ilaris® (canakinumab subcutaneous injection – Novartis)

REVIEW DATE: 01/25/2023; selected revision 09/06/2023

OVERVIEW

Ilaris, an interleukin-1β (IL-1β) blocker, is indicated for the following uses:[1]

- **Periodic Fever Syndromes:**
  - **Cryopyrin-Associated Periodic Syndromes** (CAPS), including Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS), for treatment of patients ≥ 4 years of age.
  - **Familial Mediterranean Fever** (FMF), in adult and pediatric patients.
  - **Hyperimmunoglobulin D Syndrome** (HIDS)/**Mevalonate Kinase Deficiency** (MKD), in adult and pediatric patients.
  - **Tumor Necrosis Factor Receptor Associated Periodic Syndrome** (TRAPS), in adult and pediatric patients.
- **Still's disease**, including active **Adult-Onset Still's Disease** (AOSD) and **Systemic Juvenile Idiopathic Arthritis** (SJIA), in patients ≥ 2 years of age.
- **Gout flares** for adults in whom nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate.

i.

XX) In the pivotal study for period fevers, patients were required to be at least 2 years of age with a disease flare, defined as a C-reactive protein level ≥ 10 mg/L. Prior to starting Ilaris, a minimum level of disease activity at baseline was required for familial Mediterranean fever (at least one flare per month despite colchicine), hyperimmunoglobulin D syndrome/mevalonate kinase deficiency (≥ three febrile acute flares within the previous 6 month period), and TRAPS (≥ six flares per year). In this study, patients were assessed for a response following 4 months of treatment with Ilaris.

ii.

Guidelines

Ilaris is used for a variety of periodic fever syndromes and inflammatory conditions.

- **CAPS:** A consensus protocol for hereditary autoinflammatory syndromes (2020) lists Ilaris as a treatment option across the spectrum of CAPS.[11] Continuous therapy is recommended for severe, continuous disease. For those who do not achieve remission or minimal disease activity following 1 to 3 months of treatment, dose escalation or shortened dosing interval are among the treatment options. On-demand therapy is also a treatment option for those patients who have intermittent, mild disease with low disease activity.
- **Familial Mediterranean Fever:** Guidelines for familial Mediterranean fever from the European League Against Rheumatism (2016) note that treatment goals are to prevent the clinical attacks and to suppress chronic subclinical inflammation.[6] IL-1 blockade is an option for patients with protracted febrile myalgia. In patients who develop amyloidosis, the maximal tolerated dose of colchicine and biologics (especially IL-1 blockade) are recommended.
- **Gout**: Guidelines for the management of gout flares from the American College of Rheumatology (ACR) [2020] recommend colchicine, NSAIDs, or glucocorticoids (oral, intraarticular, or intramuscular) as appropriate first-line therapy.[12] If a patient is unable to tolerate or has

contraindications to any of the first line conventional alternatives, IL-1 inhibitors are conditionally recommended.

- **Mevalonate Kinase Deficiency:** European guidelines for autoinflammatory disorders (2015) recommend consideration of short-term use of IL-1 blockers for termination of attacks and to limit or prevent steroid adverse events.[5] Maintenance therapy with an IL-1 blocker may be used in patients with mevalonate kinase deficiency and frequent attacks and/or subclinical inflammation between attacks. A consensus protocol for hereditary autoinflammatory syndromes (2020) lists Ilaris as a treatment option across the spectrum of mevalonate kinase deficiency/hyperimmunoglobulin D syndrome.[11] Continuous therapy is recommended for severe, continuous disease. For those who do not achieve remission or minimal disease activity following 1 to 3 months of treatment, dose escalation or shortened dosing interval are among the treatment options. On-demand therapy is also a treatment option for those patients who have intermittent, mild disease.
- **SJIA:** There are standardized treatment plans published for use of Ilaris.[7,8] At Month 3, patients with unchanged or worsening disease or patients whose steroid dose is > 50% of the starting dose should have an increase in prednisone plus either addition of methotrexate or change to Actemra. Guidelines from the ACR for the management of SJIA (2021) mention Ilaris as a treatment alternative, depending upon the manifestations of SJIA being treated.[9] While there are a number of other effective options for treating synovitis in patients with active SJIA, effective options for treatment of macrophage activation syndrome are much more limited and include Kineret (anakinra subcutaneous injection), calcineurin inhibitors, and systemic corticosteroids (no preferential sequencing noted). Although use of Ilaris is uncertain in some situations, macrophage activation syndrome is a potentially life-threatening situation with limited treatment options.
- **TRAPS:** European guidelines for autoinflammatory disorders (2015) note that IL-1 blockade is beneficial for the majority of patients; maintenance with IL-1 blockade, which may limit corticosteroid exposure, may be used in patients with frequent attacks and/or subclinical inflammation between attacks. A consensus protocol for hereditary autoinflammatory syndromes (2020) lists Ilaris as a treatment option across the spectrum of TRAPS.[11] Continuous therapy is recommended for severe, continuous disease. For those who do not achieve remission or minimal disease activity following 1 to 3 months of treatment, dose escalation or shortened dosing interval are among the treatment options. On-demand therapy is also a treatment option for those patients who have intermittent, mild disease.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ilaris. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ilaris as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Ilaris to be prescribed by or in consultation with a physician who specializes in the condition being treated.

All reviews for use of Ilaris for COVID-19 and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Ilaris is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Cryopyrin-Associated Periodic Syndromes (CAPS) [including Familial Cold Autoinflammatory Syndrome, Muckle-Wells Syndrome, and Neonatal Onset Multisystem Inflammatory Disease {NOMID} or Chronic Infantile Neurological Cutaneous and Articular {CINCA} Syndrome].** Approve for the duration noted if the patient meets ONE of the following (A or B):
   2. Initial Therapy. Approve for 6 months if the patient meets the following (i and ii):
   i. Patient is ≥ 4 years of age; AND
   ii. Ilaris is prescribed by or in consultation with a rheumatologist, geneticist, allergist/immunologist, or dermatologist.
   3. Patient is Currently Receiving Ilaris. Approve for 1 year if the patient meets BOTH of the following (i and ii):
   iii. Patient has been established on this medication for at least 6 months; AND
   Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).
   iv. Patient meets at least one of the following (a or b):
   a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
   Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, amyloid A), reduction in proteinuria, and/or stabilization of serum creatinine.
   b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom.
   YY) Note: Examples of improvement in symptoms include fewer cold-induced attacks; less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

ZZ)

4. **Familial Mediterranean Fever (FMF).** Approve for the duration noted if the patient meets ONE of the following (A or B):
   A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, and v):
   i. Patient is ≥ 2 years of age; AND
   ii. Patient has tried colchicine, unless contraindicated; AND
   iii. Patient will be taking Ilaris in combination with colchicine, unless colchicine is contraindicated or not tolerated; AND
   iv. Prior to starting Ilaris, the patient meets both of the following (a and b):
   a) C-reactive protein level is ≥ 10 mg/L OR elevated to at least two times the upper limit of normal for the reporting laboratory; AND
   b) Patient has a history of at least one flare per month despite use of colchicine, OR was hospitalized for a severe flare; AND
   v. The medication is prescribed by or in consultation with a rheumatologist, nephrologist, geneticist, gastroenterologist, oncologist, or hematologist.
   B) Patient is Currently Receiving Ilaris. Approve for 1 year if the patient meets BOTH of the following (i and ii):
   i. Patient has been established on this medication for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include decreased frequency of attacks, resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, amyloid A), reduction in proteinuria, and/or stabilization of serum creatinine.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom.
AAA) Note: Examples of improvement in symptoms include decreased pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

3. Gout, Acute Flare. Approve for 6 months if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient meets ONE of the following (i or ii):

iii. Patient meets BOTH of the following (a and b):

a) Patient has an intolerance, contraindication, or lack of response to nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of acute gout flares; AND

b) Patient has an intolerance, contraindication, or lack of response to colchicine for the treatment of acute gout flares; OR

iv. Patient meets BOTH of the following (a and b):

a) Patient has been previously treated with corticosteroids (oral or injectable) for an acute gout flare; AND

b) According to the prescriber, patient is unable to be retreated with a repeat course of corticosteroids (oral or injectable) for acute gout flares; AND

C) According to the prescriber, patient is receiving or will be taking concomitant urate lowering medication for the prevention of gout unless contraindicated; AND
Note: Examples of uric acid lowering drugs include allopurinol, febuxostat, or probenecid.

D) Ilaris is prescribed by or in consultation with a rheumatologist.

4. Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 2 years of age; AND

ii. Prior to starting Ilaris, the patient meets both of the following (a and b):

a) C-reactive protein level is ≥ 10 mg/L OR elevated to at least two times the upper limit of normal for the reporting laboratory; AND

b) Patient has a history of at least three febrile acute flares within the previous 6-month period OR was hospitalized for a severe flare; AND

iii. The medication is prescribed by or in consultation with a rheumatologist, nephrologist, geneticist, oncologist, or hematologist.

B) Patient is Currently Receiving Ilaris. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on this medication for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include decreased frequency of attacks, resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, amyloid A), reduction in proteinuria, and/or stabilization of serum creatinine.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom.
BBB) Note: Examples of improvement in symptoms include decreased pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

5. Stills Disease, Adult Onset. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months (which is adequate for three doses) if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND
Note: If the patient is < 18 years of age, refer to criteria for systemic juvenile idiopathic arthritis.

ii. Patient meets ONE of the following conditions (a, b, or c):

a) Patient has tried at least TWO other biologics; OR
Note: Examples of biologics include Actemra (tocilizumab intravenous infusion, tocilizumab subcutaneous injection), Kineret (anakinra subcutaneous injection), Orencia (abatacept intravenous infusion, abatacept subcutaneous injection), an etanercept product, adalimumab product, or infliximab product.

b) Patient meets BOTH of the following [(1) and (2)]:

(1) Patient has features of poor prognosis, as determined by the prescriber; AND
Note: Examples of features of poor prognosis include arthritis of the hip, radiographic damage, 6-month duration of significant active systemic disease, defined by: fever, elevated inflammatory markers, or requirement for treatment with systemic glucocorticoids.

(2) Patient has tried Actemra or Kineret; OR

c) Patient meets BOTH of the following [(1) and (2)]:

(1) Patient has active systemic features with concerns of progression to macrophage activation syndrome, as determined by the prescriber; AND

(2) Patient has tried Kineret; AND

iii. Ilaris is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Ilaris. Approve for 1 year if the patient meets BOTH of the following (i and ii):

iv. Patient has been established on this medication for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

v. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom.

CCC) Note: Examples of improvement in symptoms include less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

DDD)

6. Systemic Juvenile Idiopathic Arthritis (SJIA). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months (which is adequate for three doses) if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 2 years of age; AND

ii. Patient meets ONE of the following (a, b, or c):

a) Patient has tried at least TWO other biologics; OR

Note: Examples of biologics for SJIA include Actemra (tocilizumab intravenous infusion, tocilizumab subcutaneous injection), Kineret (anakinra subcutaneous injection), Orencia (abatacept intravenous infusion, abatacept subcutaneous injection), an etanercept product, adalimumab product, or infliximab product.

b) Patient meets BOTH of the following [(1) and (2)]:

(1) Patient has features of poor prognosis, as determined by the prescriber; AND

Note: Examples of features of poor prognosis include arthritis of the hip, radiographic damage, 6-month duration of significant active systemic disease, defined by: fever, elevated inflammatory markers, or requirement for treatment with systemic glucocorticoids.

(2) Patient has tried Actemra or Kineret; OR

c) Patient meets BOTH of the following [(1) and (2)]:

(1) Patient has features of SJIA with active systemic features with concerns of progression to macrophage activation syndrome, as determined by the prescriber; AND

(2) Patient has tried Kineret; AND

iii. Ilaris is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Ilaris. Approve for 1 year if the patient meets BOTH of the following (i and ii):

iii. Patient has been established on this medication for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

iv. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR

Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom.

Note: Examples of improvement in symptoms include less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

7. Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 2 years of age; AND

ii. Prior to starting Ilaris, the patient meets both of the following (a and b):

a) C-reactive protein level is ≥ 10 mg/L OR elevated to at least two times the upper limit of normal for the reporting laboratory; AND

b) Patient has a of at least six flares per year OR was hospitalized for a severe flare; AND

iii. The medication is prescribed by or in consultation with a rheumatologist, geneticist, nephrologist, oncologist, or hematologist.

B) Patient is Currently Receiving Ilaris. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on this medication for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR

Note: Examples of objective measures include decreased frequency of attacks, resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, amyloid A), reduction in proteinuria, and/or stabilization of serum creatinine.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom.

EEE) Note: Examples of improvements in symptoms include such as decreased pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ilaris is not recommended in the following situations:

1. **Concurrent Biologic Therapy.** Ilaris has not been evaluated and should not be administered in combination with another biologic agent for an inflammatory condition (see Appendix for examples). An increased incidence of serious infections has been associated with another IL-1 blocker, Kineret, when given in combination with tumor necrosis factor inhibitor in patients with rheumatoid arthritis. Concomitant administration of Ilaris and other agents that block IL-1 or its receptors is not recommended.

FFF)

2. **COVID-19 (Coronavirus Disease 2019).** Forward all requests to the Medical Director.
   Note: This includes requests for cytokine release syndrome associated with COVID-19.

GGG)

3. **Rheumatoid Arthritis.** Efficacy is not established. In a 12-week, Phase II, placebo-controlled, double-blind study, 277 patients who had failed methotrexate were randomized to Ilaris or placebo.[10] Although the ACR 50 at Week 12 was higher for Ilaris 150 mg (given every 4 weeks) compared with placebo (26.5% vs. 11.4%, respectively; P = not significant), there was not a statistically significant difference in ACR 50 for the other Ilaris treatment groups (Ilaris 300 mg every 2 weeks; Ilaris 600 mg loading dose followed by 300 mg every 2 weeks).

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

[*] Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Ilumya Prior Authorization Policy
- Ilumya® (tildrakizumab-asmn subcutaneous injection – Sun)

REVIEW DATE: 05/10/2023

OVERVIEW

Ilumya, an interleukin (IL)-23 blocker, is indicated for the treatment of adults with moderate to severe **plaque psoriasis** who are candidates for systemic therapy or phototherapy. It is administered subcutaneously at Weeks 0 and 4 and then once every 12 weeks thereafter. Ilumya should be administered by a healthcare professional. Safety and efficacy have not been established in patients < 18 years of age.

Guidelines

Joint guidelines from the American Academy of Dermatology and National Psoriasis Medical Board (2019) have been published for management of psoriasis with biologics.[2] These guidelines list Ilumya as a monotherapy treatment option for patients with moderate to severe plaque psoriasis. Guidelines from the European Dermatology Forum (2015) recommend biologics (i.e., etanercept, adalimumab, infliximab, Stelara® [ustekinumab subcutaneous injection]) as second-line therapy for induction and long-term treatment if phototherapy and conventional systemic agents have failed, are contraindicated, or are not tolerated.[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ilumya. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ilumya as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Ilumya to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ilumya is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Plaque Psoriasis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets ALL of the following criteria (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient meets ONE of the following (a or b):
       - **a)** Patient has tried at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR
         Note: Examples of one traditional systemic agent include methotrexate, cyclosporine, acitretin tablets, or psoralen plus ultraviolet A light (PUVA). An exception to the

requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already had a 3-month trial or previous intolerance to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for plaque psoriasis. A patient who has already tried a biologic for psoriasis is not required to "step back" and try a traditional systemic agent for psoriasis.

b) Patient has a contraindication to methotrexate, as determined by the prescriber; AND

iii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Ilumya. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has been established on therapy for at least 90 days; AND
Note: A patient who has received < 90 days of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating the requested drug) in at least one of the following: estimated body surface area, erythema, induration/thickness, and/or scale of areas affected by psoriasis; AND

iii. Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain, itching, and/or burning.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ilumya is not recommended in the following situations:

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1. **Concurrent Use with other Biologics or with Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs).** Data are lacking evaluating concomitant use of Ilumya with another biologic or with a targeted synthetic DMARD for an inflammatory condition (see Appendix for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher rate of adverse effects and lack controlled trial data in support of additive efficacy.[4]
   Note: This does NOT exclude the use of methotrexate (a traditional systemic agent used to treat psoriasis) in combination with Ilumya.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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3. Nast A, Gisondi P, Ormerod AD, et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris – Update 2015 – Short version – EDF in cooperation with EADV and IPC. *J Eur Acad Dermatol Venereol*. 2015;29(12):2277-2294.
4. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *Lancet*. 2017;390(10091):276-288.

APPENDIX

[*] Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARDs – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis.

xxviii. PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Infliximab Intravenous Products Prior Authorization Policy
- Avsola™ (infliximab-axxq intravenous infusion – Amgen)
- Inflectra® (infliximab-dyyb intravenous infusion – Hospira/Pfizer)
- Infliximab intravenous infusion – Janssen/Johnson & Johnson
- Remicade® (infliximab intravenous infusion – Janssen/Johnson & Johnson)
- Renflexis® (infliximab-abda intravenous infusion – Samsung Bioepis/Merck)

REVIEW DATE: 11/15/2023

OVERVIEW

Infliximab products are tumor necrosis factor inhibitors (TNFis) approved for the following indications:[1-3]
- **Ankylosing spondylitis**, for reducing signs and symptoms of active disease.
- **Crohn's disease**, for the following uses:
  - Reducing the signs and symptoms and inducing and maintaining clinical remission in patients ≥ 6 years of age with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy; AND
  - Reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adults with fistulizing Crohn's disease.
- **Plaque psoriasis**, for treatment of adults with chronic severe (i.e., extensive and/or disabling) disease who are candidates for systemic therapy and when other systemic therapies are less appropriate.
- **Psoriatic arthritis**, for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage and improving physical function.
- **Rheumatoid arthritis**, in combination with methotrexate for reducing signs and symptoms, inhibiting the progression of structural damage and improving physical function in patients with moderately to severely active disease.
- **Ulcerative colitis**, for the following uses:
  - Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adults with moderately to severely active disease who have had an inadequate response to conventional therapy; AND
  - Reducing signs and symptoms and inducing and maintaining clinical remission in patients ≥ 6 years of age with moderately to severely active disease who have had an inadequate response to conventional therapy.

Avsola, Inflectra, and Renflexis were approved as biosimilar to Remicade, indicating no clinically meaningful differences in safety and effectiveness and the same mechanism of action, route of administration, dosage form, and strength as Remicade.[2-3] However, minor differences in clinically inactive components are allowed. At this time, only biosimilarity has been demonstrated (not interchangeability).

Guidelines

TNFis feature prominently in guidelines for treatment of many inflammatory conditions.
- **Ankylosing Spondylitis and Non-Radiographic Spondyloarthritis:** Guidelines for ankylosing spondylitis and non-radiographic axial spondyloarthritis are published by the American College of Rheumatology (ACR)/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019).[4] Following primary nonresponse to a TNFi, an interleukin (IL)-17 blocker is recommended; however, if the patient is a secondary nonresponder, a second TNFi is

recommended over switching out of the class. In patients with a contraindication to a TNFi, use of an IL-17 blocker is recommended over traditional oral agents such as methotrexate or sulfasalazine.

- **Crohn's Disease:** The American College of Gastroenterology (ACG) has guidelines for Crohn's disease (2018).[5] TNFis are listed as an option for disease that is resistant to corticosteroids, severely active disease, perianal fistulizing disease, and maintenance of remission. In post-operative Crohn's disease, a TNFi should be started within 4 weeks of surgery to prevent recurrence. Guidelines from the American Gastroenterological Association (AGA) [2021] include infliximab among the therapies for moderate to severe Crohn's disease, for induction and maintenance of remission.[6]
- **Plaque Psoriasis:** Guidelines from the American Academy of Dermatologists (AAD) and National Psoriasis Foundation (NPF) [2019] recommend infliximab as a monotherapy treatment option for adults with moderate to severe disease.[7]
- **Psoriatic Arthritis:** Guidelines from ACR (2019) recommend TNFis over other biologics for use in treatment-naïve patients with psoriatic arthritis, and in those who were previously treated with an oral therapy.[8]
- **Rheumatoid Arthritis:** Guidelines from ACR (2021) recommend addition of a biologic or a targeted synthetic disease modifying anti-rheumatic drug (DMARD) for a patient taking the maximum tolerated dose of methotrexate who is not at target.[9]
- **Ulcerative Colitis:** Updated ACG guidelines for ulcerative colitis (2019) note that the following agents can be used for induction of remission in moderately to severely active disease: budesonide extended-release tablets; oral or intravenous systemic corticosteroids, Entyvio® (vedolizumab intravenous infusion), Xeljanz®/XR (tofacitanib tablets/extended-release tablets), or TNFis.[10] In addition to the approved indication, clinical guidelines for the management of pouchitis, published in 2009 indicate that first-line therapy for pouchitis is antibiotic therapy (e.g. metronidazole, ciprofloxacin).[11] Other treatment options include maintenance probiotics, oral or topical budesonide, anti-inflammatory drugs (e.g., mesalamine), or immunosuppressive drugs (e.g., infliximab). Guidelines from the AGA (2020) recommend infliximab for moderate to severe ulcerative colitis.[12]
- **Behcet's Disease:** The European League Against Rheumatism (EULAR) recommendations (2018) include TNFis for initial or recurrent sight-threatening uveitis.[13] For patients refractory to first-line treatments (e.g., corticosteroids), TNFis are among the treatment options for mucocutaneous manifestations, venous thrombosis, severe or refractory gastrointestinal disease, and recurrent/chronic joint involvement. Recommendations for the use of TNFis in ocular inflammatory disorders from the American Academy of Ophthalmology (AAO) [2014] note that TNFis may be used first-line in patients with ophthalmic manifestations of Behcet's disease and for acute exacerbations of pre-existing Behcet's disease.[14]
- **Graft-Versus-Host Disease:** Guidelines from the National Comprehensive Cancer network (NCCN) [version 3.2023 – October 9, 2023] list infliximab among the agents used for steroid-refractory disease.[15]
- **Hidradenitis Suppurativa:** Guidelines from the US and Canadian Hidradenitis Suppurativa Foundations make recommendations for topical, intralesional, and systemic medical management of disease.[16] For acute lesions of all stages, antiseptic washes, short-term oral steroids, and interlesional steroids are among the recommendations. Systemic antibiotics have been a mainstay of treatment. Infliximab is a recommended therapy for moderate to severe disease.
- **Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitors:** NCCN has guidelines (version 3.2023 – October 11, 2023) for Management of Immunotherapy-Related Toxicities.[17] Infliximab is recommended among the alternatives to manage steroid-refractory inflammatory arthritis, vision changes, myocarditis, pericarditis, acute kidney injury (e.g., azotemia, creatinine elevation, inability to maintain acid/base or electrolyte balance, urine output change), pneumonitis, myalgia, or myositis, and diarrhea/colitis. Additionally, the guidelines also

note that infliximab should not be used to treat hepatitis associated with an immunotherapy-related toxicity.

- **Indeterminate Colitis:** Infliximab has been effective in some patients with refractory indeterminate colitis (retrospective reviews).[18,19] When patients who are refractory to standard therapy can be definitively classified as having ulcerative colitis, colectomy is considered an effective long-term surgical treatment. Patient's with Crohn's disease, however, have a high risk of complications after ileal pouch-anal anastomosis and are treated more aggressively with medical interventions since surgical options cannot offer the same likelihood of success as in ulcerative colitis.
- **Juvenile Idiopathic Arthritis (JIA):** There are guidelines from ACR and the Arthritis Foundation for the treatment of JIA (2021) which address oligoarthritis and temporomandibular joint (TMJ) arthritis.[20] For oligoarthritis, a biologic is recommended following a trial of a conventional synthetic DMARD. In patients with TMJ arthritis, scheduled nonsteroidal anti-inflammatory drugs (NSAIDs) and/or intra-articular glucocorticoids are recommended first-line. A biologic is a therapeutic option if there is an inadequate response or intolerance. Additionally, rapid escalation to a biologic ± conventional synthetic DMARD (methotrexate preferred) is often appropriate given the impact and destructive nature of TMJ arthritis. In these guidelines, there is not a preferred biologic that should be initiated for JIA. The ACR/Arthritis Foundation Guideline for the treatment of JIA (2019) provides updated recommendations for juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis.[21] Infliximab is among the TNFis recommended as subsequent therapy following treatment with a conventional synthetic DMARD such as methotrexate. TNF antagonists such as infliximab may also be used as second- or third-line treatment for systemic JIA.[22]
- **Ocular Inflammatory Disorders:** Recommendations for the use of TNFis in ocular inflammatory disorders from the AAO (2014) note that infliximab may be used as second-line corticosteroid-sparing therapy for chronic and severe scleritis.[14] Infliximab may be used in patients with uveitis due to various causes (e.g., spondyloarthropathy-associated or human leukocyte antigen [HLA]-B27-associated uveitis, juvenile idiopathic arthritis-associated uveitis, and other posterior uveitides and panuveitis syndromes). Infliximab should be considered second-line in vision-threatening JIA-associated uveitis when methotrexate has failed or is not tolerated (strong recommendation) and vision-threatening chronic uveitis from seronegative spondyloarthropathy (strong recommendation). Infliximab may also be considered in other patients who have vision-threatening or corticosteroid-dependent disease who have failed first-line therapies. The recommendations point out that studies evaluating infliximab in uveitis included patients with birdshot chorioretinitis (BSCR), a bilateral posterior uveitis generally treated with systemic immunomodulation; these patients showed a good response to infliximab.
- **Pyoderma Gangrenosum:** Although guidelines are not current, multiple topical and systemic therapies have been used for pyoderma gangrenosum. Oral prednisone is the most common initial immunosuppressant medication.[23] Other systemic therapies include cyclosporine, methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, and TNFis (i.e., infliximab, etanercept, and adalimumab products). In case reports, TNFis have been effective.
- **Sarcoidosis:** The European Respiratory Society Task Force has guidelines for treatment of pulmonary, cutaneous, cardiac, and neurologic sarcoidosis.[24] Infliximab is a recommended therapy after continued disease or relapse while taking systemic corticosteroids and immunosuppressants (e.g., methotrexate, azathioprine, leflunomide, mycophenolate mofetil, hydroxychloroquine).
- **Still's Disease:** Still's disease presents in adults with features similar to those of systemic onset JIA.[25,26] In case series, infliximab has been effective in patients with Still's disease that was refractory to therapy with corticosteroids, methotrexate, azathioprine, and cyclophosphamide.[27]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of infliximab products. Because of the specialized skills required for evaluation and diagnosis of a patient treated with infliximab as well as

the monitoring required for adverse events and long-term efficacy, initial approval requires infliximab to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration listed below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of infliximab intravenous products is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Ankylosing Spondylitis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist.
   - **B)** Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):
     - **i.** Patient has been established on therapy for at least 6 months; AND
       Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).
     - **ii.** Patient meets at least one of the following (a or b):
       - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR
         Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondyloarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).
       - **b)** Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

2. **Crohn's Disease.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, and iii):
     - **i.** Patient is ≥ 6 years of age; AND
     - **ii.** Patient meets ONE of the following (a, b, c, or d):
       - **a)** Patient has tried or is currently taking corticosteroids, or corticosteroids are contraindicated in this patient; OR
         - Note: Examples of corticosteroids are prednisone and methylprednisolone.
       - **b)** Patient has tried one other conventional systemic therapy for Crohn's disease; OR
         Note: Examples of conventional systemic therapies for Crohn's disease include azathioprine, 6-mercaptopurine, or methotrexate. An exception to the requirement for a trial of or contraindication to steroids or a trial of one other conventional systemic agent can be made if the patient has already tried at least one biologic other than the requested medication A biosimilar of the requested biologic does not count. Refer to Appendix for

examples of biologics used for Crohn's disease. A trial of mesalamine does not count as a systemic therapy for Crohn's disease.

c) Patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas; OR

d) Patient had ileocolonic resection (to reduce the chance of Crohn's disease recurrence); AND

iii. The medication is prescribed by or in consultation with a gastroenterologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

e) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR

- Note: Examples of objective measures include fecal markers (e.g., fecal lactoferrin, fecal calprotectin), serum markers (e.g., C-reactive protein), imaging studies (magnetic resonance enterography [MRE], computed tomography enterography [CTE]), endoscopic assessment, and/or reduced dose of corticosteroids.

f) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or blood in stool.

3. Plaque Psoriasis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets ONE of the following (a or b):

a) Patient has tried at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR
Note: Examples include methotrexate, cyclosporine, acitretin (Soriatane®, generics), or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient already had a 3-month trial or previous intolerance to at least one biologic other than the requested medication. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for psoriasis. A patient who has already tried a biologic for psoriasis is not required to "step back" and try a traditional systemic agent for psoriasis.

b) Patient has a contraindication to methotrexate, as determined by the prescriber; AND

iii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has been established on therapy for at least 90 days; AND
Note: A patient who has received < 90 days of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

ii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating an infliximab product) in at least one of the following: estimated body surface area affected, erythema, induration/thickness, and/or scale of areas affected by psoriasis; AND

4. Compared with baseline (prior to receiving an infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain, itching, and/or burning.

Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

xxix. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

xxx. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR

- Note: Examples of objective measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsA DAS), Grace Index, Leeds Enthesitis Score (LEI), Spondyloarthritis Consortium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; or decreased soft tissue swelling in joints or tendon sheaths.

5. Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND

Note: Examples include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient already had a 3-month trial of at least one biologic other than the requested medication. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for rheumatoid arthritis. A patient who has already tried a biologic is not required to "step back" and try a conventional synthetic DMARD.

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

v. Patient has been established on therapy for at least 6 months; AND

- Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

vi. Patient meets at least one of the following (a or b):

f) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR

Note: Examples of objective measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate or C-reactive protein, Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).

- **b)** Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; or decreased soft tissue swelling in joints or tendon sheaths.

6. Ulcerative Colitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, and iii):

i. Patient is ≥ 6 years of age; AND

ii. Patient meets ONE of the following (a or b):

a) Patient had a trial of one systemic agent or was intolerant to one of these agents for ulcerative colitis; OR

Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone or methylprednisolone. A trial of a mesalamine product does not count as a systemic therapy for ulcerative colitis. A previous trial of one biologic other than the requested medication also counts as a trial of one systemic agent for ulcerative colitis. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for ulcerative colitis.

b) Patient meets BOTH of the following [(1) and (2)]:

(1) Patient has pouchitis; AND

(2) Patient has tried therapy with an antibiotic, probiotic, corticosteroid enema, or Rowasa® (mesalamine enema); AND

Note: Examples of antibiotics include metronidazole and ciprofloxacin. Examples of corticosteroid enemas include hydrocortisone enema (Cortenema, generics).

iii. The medication is prescribed by or in consultation with a gastroenterologist.

C) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

ii. Patient has been established on therapy for at least 6 months; AND

- Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR

- Note: Examples of objective measures include fecal markers (e.g., fecal calprotectin), serum markers (e.g., C-reactive protein), endoscopic assessment, and/or reduced dose of corticosteroids.

c) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or rectal bleeding.

Other Uses with Supportive Evidence

7. Behcet's Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii):

i. Patient meets ONE of the following (a or b):

a) Patient has tried at least ONE conventional therapy; OR

- Note: Examples include systemic corticosteroids (e.g., methylprednisolone), immunosuppressants (azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, tacrolimus, Leukeran® [chlorambucil tablet], cyclophosphamide, interferon alfa). An exception to the requirement for a trial of one conventional therapy can be made if the patient has already had a trial of at least one tumor necrosis factor inhibitor (e.g., an adalimumab product, an etanercept product). A patient who has already tried one biologic

other than the requested drug for Behcet's disease is not required to "step back" and try a conventional therapy. A biosimilar of the requested biologic does not count.

b) Patient has ophthalmic manifestations of Behcet's disease; AND

ii. The medication is prescribed by or in consultation with a rheumatologist, dermatologist, ophthalmologist, gastroenterologist, or neurologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has been established on therapy for at least 90 days; AND

- Note: A patient who has received < 90 days of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

ii. When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); AND

- Note: Examples of objective measures are dependent upon organ involvement but may include best-corrected visual acuity (if ophthalmic manifestations); serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate); or ulcer depth, number, and/or lesion size.

iii. Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain or improved visual acuity (if ophthalmic manifestations).

8. Graft-Versus-Host Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month if the patient meets BOTH of the following (i and ii):

i. Patient has tried at least one conventional systemic treatment for graft-versus-host disease; AND

Note: Examples of conventional treatments include corticosteroids (e.g., methylprednisolone), antithymocyte globulin, cyclosporine, tacrolimus, and mycophenolate mofetil.

ii. The medication is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center; OR

B) Patient is Currently Receiving an Infliximab Product. Approve for 3 months if the patient meets BOTH of the following (i and ii):

iii. Patient has been established on an infliximab product for at least 1 month; AND

- Note: A patient who has received < 1 month of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

iv. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR

- Note: An example of objective measures is normalization of liver function tests, red blood cell count, or platelet count, or resolution of fever or rash.

b) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as improvement in skin, oral mucosal, ocular, or gastrointestinal symptoms (e.g., nausea, vomiting, anorexia).

9. Hidradenitis Suppurativa. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii):

i. Patient has tried one other therapy; AND

HHH) Note: Examples include intralesional or oral corticosteroids (e.g., triamcinolone, prednisone), systemic antibiotics (e.g., clindamycin, dicloxacillin, erythromycin), and isotretinoin.

ii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

vii. Patient has been established on therapy for at least 90 days; AND

- Note: A patient who has received < 90 days of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

viii. When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); AND

- Note: Examples of objective measures include Hurley staging, Sartorius score, Physician Global Assessment, and Hidradenitis Suppurativa Severity Index.

ix. Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain or drainage of lesions, nodules, or cysts.

10. Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy. Approve for the duration noted if the patient meets ONE of the following (A or B):

C) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, and iv):

i. Patient developed an immunotherapy-related toxicity other than hepatitis; AND
Note: For example, gastrointestinal system toxicity (e.g., colitis), ocular toxicity (e.g., uveitis/iritis, episcleritis, and blepharitis). myocarditis, pericarditis, inflammatory arthritis, acute kidney injury (e.g., azotemia, creatinine elevation, inability to maintain acid/base or electrolyte balance, urine output change), pneumonitis, myalgia, or myositis.

ii. Patient developed this immune-related toxicity while receiving a checkpoint inhibitor; AND
Note: Examples of checkpoint inhibitors include Keytruda (pembrolizumab intravenous [IV] infusion), Opdivo (nivolumab IV infusion), Yervoy (ipilimumab IV infusion), Tecentriq (atezolizumab IV infusion), Bavencio (avelumab IV infusion), or Imfinzi (durvalumab IV infusion).

iii. Patient has tried one systemic corticosteroid; AND
Note: Examples include methylprednisone and prednisone.

iv. The medication is prescribed by or in consultation with an oncologist, gastroenterologist, rheumatologist, or ophthalmologist; OR

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR
Note: Examples of objective measures are dependent upon organ involvement but may include clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), fecal markers (e.g., fecal calprotectin), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as less joint pain/tenderness, stiffness or swelling (if joint symptoms), stool frequency and/or rectal bleeding (if gastrointestinal symptoms), and/or improved function or activities of daily living.

11. Indeterminate Colitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

III) Note: Indeterminate colitis is defined as colitis that cannot be classified with certainty as either ulcerative colitis or Crohn's disease.

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, and v):

i. Patient is ≥ 6 years of age; AND

ii. Patient has tried one systemic corticosteroid; AND

JJJ) Note: Examples include prednisone and methylprednisolone.

iii. Patient has tried mesalamine; AND

iv. Patient has tried either azathioprine or 6-mercaptopurine; AND

v. The medication is prescribed by or in consultation with a gastroenterologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

iii. Patient has been established on therapy for at least 6 months; AND

- Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR

- Note: Examples of objective measures include fecal markers (e.g., fecal calprotectin), serum markers (e.g., C-reactive protein), endoscopic assessment, and/or reduced dose of corticosteroids.

b) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or rectal bleeding.

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12. Juvenile Idiopathic Arthritis (JIA). Approve for the duration noted if the patient meets ONE of the following (A or B):

KKK) Note: This includes JIA regardless of type of onset, including a patient with juvenile spondyloarthropathy/active sacroiliac arthritis. JIA is also referred to as Juvenile Rheumatoid Arthritis.

A) Initial Therapy. Approve for 6 months if the patient meets the following (i and ii):

i. Patient meets ONE of the following (a or b):

a) Patient has tried one other systemic medication for this condition; OR

~~**LLL)**~~ Note: Examples of other medications for JIA include methotrexate, sulfasalazine, or leflunomide, a nonsteroidal anti-inflammatory drug (NSAID) [e.g., ibuprofen, naproxen]. A previous trial of one biologic other than the requested medication also counts as a trial of one medication. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for JIA.

b) Patient has aggressive disease, as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR

Note: Examples of objective measures include Physician Global Assessment (MD global), Parent/Patient Global Assessment of Overall Well-Being (PGA), Parent/Patient Global Assessment of Disease Activity (PDA), Juvenile Arthritis Disease Activity Score (JDAS), Clinical Juvenile Arthritis Disease Activity Score (cJDAS), Juvenile Spondyloarthritis Disease Activity Index (JSpADA), serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

c) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as improvement in limitation of motion, less joint pain or tenderness, decreased duration of morning stiffness or fatigue, or improved function or activities of daily living.

13. Pyoderma Gangrenosum. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets BOTH of the following (i and ii):

i. Patient meets ONE of the following (a or b):

A) Patient has tried one systemic corticosteroid; OR

Note: Examples include prednisone and methylprednisolone.

B) Patient has tried one other immunosuppressant for at least 2 months or was intolerant to one of these medications; AND

Note: Examples include mycophenolate mofetil and cyclosporine.

ii. The medication is prescribed by or in consultation with a dermatologist; OR

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

vii. Patient has been established on therapy for at least 4 months; AND

- Note: A patient who has received < 4 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

viii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating an infliximab product) in at least one of the following: size, depth, and/or number of lesions; AND

ix. Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain and/or tenderness of affected lesions.

14. Sarcoidosis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient has tried at least one corticosteroid; AND

Note: Examples include prednisone and methylprednisolone.

ii. Patient has tried at least one immunosuppressive medication; AND

Note: Examples include methotrexate, azathioprine, leflunomide, mycophenolate mofetil, hydroxychloroquine, or chloroquine.

iii. The medication is prescribed by or in consultation with a pulmonologist, ophthalmologist, cardiologist, neurologist, or dermatologist; OR

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

iv. Patient has been established on therapy for at least 90 days; AND

- Note: A patient who has received < 90 days of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

v. When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); AND

- Note: Examples of objective measures are dependent upon organ involvement but may include lung function (e.g., predicted forced vital capacity and/or 6-minute walk distance); serum markers (e.g., C-reactive protein, liver enzymes, N-terminal pro-brain natriuretic peptide [NT-proBNP]); improvement in rash or skin manifestations, neurologic symptoms, or rhythm control; or imaging (e.g., if indicated, chest radiograph, magnetic resonance imaging [MRI], or echocardiography).

vi. Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased cough, fatigue, pain, palpitations, neurologic symptoms, and/or shortness of breath.

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15. Scleritis or Sterile Corneal Ulceration. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient has tried one other therapy for this condition; AND

- Note: Examples include oral non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin; oral, topical (ophthalmic) or intravenous corticosteroids (such as prednisone, prednisolone, methylprednisolone); methotrexate; cyclosporine; or other immunosuppressants.

ii. The medication is prescribed by or in consultation with an ophthalmologist; OR

C) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

ii. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR

- Note: Examples of objective measures are serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

c) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased eye pain, redness, light sensitivity, tearing, and/or improvement in visual acuity.

16. Spondyloarthritis, Other Subtypes Approve for the duration noted if the patient meets ONE of the following (A or B):

- Note: Examples of other subtypes include undifferentiated arthritis, non-radiographic axial spondylitis, Reactive Arthritis [Reiter's disease]. For ankylosing spondylitis or psoriatic arthritis, refer to the respective criteria under FDA-approved indications.

G) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient meets ONE of the following (a or b):

a) Patient has arthritis primarily in the knees, ankles, elbows, wrists, hands, and/or feet AND has tried at least ONE conventional synthetic disease-modifying antirheumatic drug (DMARD); OR

- Note: Examples include methotrexate, leflunomide, and sulfasalazine.

b) Patient has axial spondyloarthritis with objective signs of inflammation, defined as at least one of the following [(1) or (2)]:

(1) C-reactive protein elevated beyond the upper limit of normal for the reporting laboratory; OR

(2) Sacroiliitis reported on magnetic resonance imaging; AND

ii. The medication is prescribed by or in consultation with a rheumatologist; OR

H) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

xx. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

xxi. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR

Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS) and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

17. Still's Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient has tried one corticosteroid; AND

- Note: Examples include prednisone and methylprednisolone.

ii. Patient has tried one conventional synthetic disease-modifying antirheumatic drug (DMARD) given for at least 2 months or was intolerant; AND

- Note: An example is methotrexate. A previous trial of one biologic other than the requested drug (e.g., Actemra [tocilizumab intravenous injection, tocilizumab subcutaneous injection], Arcalyst [rilonacept subcutaneous injection], Ilaris [canakinumab subcutaneous injection]) also counts towards this requirement for previous therapy for Still's disease. A biosimilar of the requested biologic does not count.

iii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

vi. Patient has been established on an this medication for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

vii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR

Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

18. Uveitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

Note: This includes other posterior uveitides and panuveitis syndromes.

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient has tried one of the following therapies: periocular, intraocular, or systemic corticosteroids, or immunosuppressives; AND

- Note: Examples of corticosteroids include prednisolone, triamcinolone, betamethasone, methylprednisolone, prednisone. Examples of immunosuppressives include methotrexate,

mycophenolate mofetil, and cyclosporine. An exception to the requirement for a trial of one of these therapies can be made if the patient has already had a trial of an etanercept product or an adalimumab product for uveitis. A patient who has already tried one biologic other than the requested medication also counts. A biosimilar of the requested biologic does not count.

ii. The medication is prescribed by or in consultation with an ophthalmologist.

C) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR

- Note: Examples of objective measures include best-corrected visual acuity, assessment of chorioretinal and/or inflammatory retinal vascular lesions, or anterior chamber cell grade or vitreous haze grade.

c) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased eye pain, redness, light sensitivity, and/or blurred vision; or improvement in visual acuity.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of infliximab intravenous products is not recommended in the following situations:

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1. Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD). Data are lacking evaluating concomitant use of an infliximab product in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see APPENDIX for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher rate of AEs and lack controlled trial data in support of additive efficacy.

Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with an infliximab product.

MMM)

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

* Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; PMR – Polymyalgia rheumatic; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Kevzara Prior Authorization Policy
- Kevzara® (sarilumab subcutaneous injection – Regeneron/Sanofi-Aventis)

REVIEW DATE: 03/08/2023

OVERVIEW

Kevzara, an interleukin-6 receptor inhibitor, is indicated for the treatment of the following conditions:[1]

- **Rheumatoid arthritis**, in adults with moderate to severe active disease who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs).
- **Polymyalgia rheumatica**, in adults who have had an inadequate response to corticosteroids or who cannot tolerate corticosteroid taper.

Guidelines

Kevzara is addressed in the following guidelines:

- **Rheumatoid Arthritis:** Guidelines from the American College of Rheumatology (ACR) [2021] recommend addition of a biologic or a targeted synthetic DMARD for a patient taking the maximum tolerated dose of methotrexate who is not at target.[2]
- **Polymyalgia Rheumatica:** Guidelines from the European League Against Rheumatism (EULAR)/ACR (2015) were published prior to approval of Kevzara of this condition.[7] The minimum effective individualized duration of glucocorticosteroid therapy is strongly recommended.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Kevzara. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kevzara as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Kevzara to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the approval duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

All reviews for use of Kevzara for Coronavirus Disease 2019 **(**COVID-19) and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kevzara is recommended in those who meet the following criteria:

FDA-Approved Indication

7. **Rheumatoid Arthritis.** Approve for the duration noted if the patient meets ONE of the following criteria (A or B):
   A) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i and ii):

i. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND
Note: Examples of conventional synthetic DMARDs include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already had a 3-month trial of at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for rheumatoid arthritis. A patient who has already tried a biologic is not required to "step back" and try a conventional synthetic DMARD.

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Kevzara. Approve for 1 year if the patient meets BOTH of the following (i and ii):

vi. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

vii. Patient meets at least one of the following (a or b):

g) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
Note: Examples of objective measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).

b) Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

8. Polymyalgia Rheumatica. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient has tried one systemic corticosteroid; AND
Note: An example of a systemic corticosteroid is prednisone.

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Kevzara. Approve for 1 year if the patient meets BOTH of the following (i and ii):

v. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

vi. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Kevzara); OR
Note: Examples of objective measures are serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), resolution of fever, and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating Kevzara), patient experienced an improvement in at least one symptom, such as decreased shoulder, neck, upper arm, hip, or thigh pain or stiffness; improved range of motion; and/or decreased fatigue.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kevzara is not recommended in the following situations:

4. **Ankylosing Spondylitis.** In a Phase II study, Kevzara did not demonstrate efficacy in patients with ankylosing spondylitis.[3]

5. **Concurrent Use with a Biologic or with a Targeted Synthetic DMARD.** Kevzara should not be administered in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see Appendix for examples). Combination therapy is generally not recommended due to a potential for a higher rate of adverse effects with combinations and lack of evidence for additive efficacy.
   Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Kevzara.

3. **COVID-19 (Coronavirus Disease 2019).** Forward all requests to the Medical Director.[4-6]
   Note: This includes requests for cytokine release syndrome associated with COVID-19.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

[*] Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Kineret Prior Authorization
- Kineret® (anakinra subcutaneous injection – Swedish Orphan Biovitrim)

REVIEW DATE: 01/25/2023

OVERVIEW

Kineret, an interleukin-1 (IL-1) receptor antagonist, indicated for the following uses:[1]
- **Cryopyrin-associated periodic syndromes** (CAPS) for treatment of neonatal-onset multisystem inflammatory disease (NOMID).
- **Deficiency of interleukin-1 receptor antagonist** (DIRA) – treatment.
- **Rheumatoid arthritis**, to reduce the signs and symptoms and slow the progression of structural damage in adult patients with moderately to severely active disease who have failed one or more disease-modifying antirheumatic drugs (DMARDs) given ± DMARDs other than tumor necrosis factor inhibitors (TNFis).

In addition to the FDA-approved uses, Kineret has been granted Emergency Use Authorization for treatment of Coronavirus disease 2019 (COVID-19) in hospitalized adults with positive viral testing with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR).[22]

Guidelines

A) IL-1 blockers are used for treatment of multiple inflammatory conditions:
- **CAPS:** CAPS encompasses three rare genetic syndromes (familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and NOMID or chronic infantile neurological cutaneous and articular syndrome) that are thought to be one condition along a spectrum of disease severity.[2,3] In many cases, patients with CAPS reported an immediate clinical response to Kineret with rash, fever, and arthritis disappearing within a few days and not recurring during follow-up.[4] Dramatic and persistent normalization of inflammatory markers and hematologic tests have also been achieved.
- **DIRA:** Dysregulation of IL-1 signaling is prominent among autoinflammatory conditions such as DIRA. Thus, Kineret has been successfully used and is indicated to treat DIRA. The approval was based on a natural- study in nine patients (aged 1 month to 9 years at baseline) with genetically confirmed DIRA.[1] Patients were treated with Kineret for up to 10 years. All nine patients achieved remission while on Kineret for DIRA. In some patients, skin and bone manifestations resolved within days and weeks, respectively.
- **Rheumatoid Arthritis:** Current recommendations for the treatment of rheumatoid arthritis from the American College of Rheumatology (ACR) [2015] do not make a recommendation for the use of Kineret.[5] The recommendations also note that Kineret is used infrequently for rheumatoid arthritis and that TNFis and other non-TNFi biologics (i.e., rituximab, Actemra® [tocilizumab intravenous infusion, tocilizumab subcutaneous injection], and Orencia® [abatacept intravenous infusion, abatacept subcutaneous injection]) are appropriate initial biologic therapy for most patients with rheumatoid arthritis.
- **Systemic Juvenile Idiopathic Arthritis (SJIA):** The 2013 update of the 2011 ACR recommendations for the treatment of SJIA advise Kineret as appropriate initial therapy in SJIA for patients with active systemic features and varying degrees of synovitis. Kineret is also

considered an appropriate second- and third-line agent for all patients with SJIA (in patients with and without active systemic features). Macrophage activation syndrome is a severe and potentially lethal complication associated with SJIA.[7] Case series have shown rapid remission of macrophage activation syndrome as well as treatment of the underlying condition with the use of Kineret.

- **Still's Disease:** Still's disease presents in adults with features similar to those of SJIA.[8] As in SJIA, Kineret has been effective in reducing fever, symptoms, and markers of inflammation in patients with adult-onset Still's disease who were refractory to conventional treatment with a corticosteroid, nonsteroidal anti-inflammatory drug (NSAID), and/or conventional synthetic DMARDs such as methotrexate.[9-14]
- **COVID-19:** Guidelines from ACR recommend consideration of Kineret (>4 mg/kg/day) for children with hyperinflammation refractory to intravenous immunoglobulin and glucocorticoids, or in patients with contraindications to long-term use of glucocorticoids.[23] Kineret is also recommended in a similar population of children with multisystem inflammatory syndrome and features of macrophage activation syndrome associated with COVID-19.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Kineret. All approvals are for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kineret as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Kineret to be prescribed by or in consultation with a physician who specializes in the condition being treated.

B) All reviews for use of Kineret for COVID-19 and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kineret is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Cryopyrin-Associated Periodic Syndromes.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):
     - **i.** The medication is being used for treatment of neonatal onset multisystem inflammatory disease (NOMID), familial cold autoinflammatory syndrome (FCAS), Muckle-Wells Syndrome (MWS), and/or chronic infantile neurological cutaneous and articular (CINCA) syndrome; AND
     - **ii.** The medication is prescribed by or in consultation with a rheumatologist, geneticist, or a dermatologist.
   - **B)** Patient is Currently Receiving Kineret. Approve for 1 year if the patient meets BOTH of the following (i and ii):
     - **v.** Patient has been established on this medication for at least 6 months; AND
       Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).
     - **vi.** Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, amyloid A), reduction in proteinuria, and/or stabilization of serum creatinine.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as fewer cold-induced attacks; less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

x.

2. Deficiency of Interleukin-1 Receptor Antagonist. Approve for the duration noted if the patient meets one of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Genetic testing has confirmed a mutation in the *IL1RN* gene; AND

ii. The medication is prescribed by or in consultation with a rheumatologist, geneticist, dermatologist, or a physician specializing in the treatment of autoinflammatory disorders.

B) Patient is Currently Receiving Kineret. Approve for 1 year if the patient meets BOTH of the following (i and ii):

xi. Patient has been established on this medication for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

xii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), reduction in proteinuria, and/or stabilization of serum creatinine.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as improvement of skin or bone symptoms; less joint pain/tenderness, stiffness, or swelling.

xiii.

3. Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

C) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following criteria (i and ii):

i. Patient has had a 3-month trial of a biologic OR targeted synthetic disease-modifying antirheumatic drug (DMARD) for this condition, unless intolerant; AND
vii. Note: This is a 3-month trial of at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics and targeted synthetic DMARDs used for rheumatoid arthritis. Conventional synthetic DMARDs such as methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine do not count.

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Kineret. Approve for 1 year if the patient meets BOTH of the following (i and ii):

viii. Patient has been established on therapy for at least 6 months; AND
xiv. Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

viii. Patient meets at least one of the following (a or b):

h) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR

Note: Examples of standardized and validated measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).

xv. b) Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

Other Uses with Supportive Evidence

D)

4. COVID-19 (Coronavirus Disease 2019). Forward all requests to the Medical Director.

Note: This includes requests for cytokine release syndrome associated with COVID-19.
Kineret has been granted Emergency Use Authorization (EUA) for treatment of Coronavirus disease 2019 (COVID-19) in hospitalized adults with positive viral testing with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR).[22] The recommended dose under the EUA is 100 mg daily by subcutaneous injection for 10 days.

Additionally, guidelines from ACR recommend consideration of Kineret (>4 mg/kg/day) for children with COVID-19 and hyperinflammation refractory to intravenous immunoglobulin and glucocorticoids, or in patients with contraindications to long-term use of glucocorticoids.[23] Initiation of Kineret prior to invasive mechanical ventilation may be beneficial. Kineret is also recommended in a similar population of children with multisystem inflammatory syndrome and features of macrophage activation syndrome associated with COVID-19. Per these guidelines, a prolonged course of immunomodulatory treatment extending for 2 or 3 weeks or longer may be necessary to avoid rebound inflammation.

E)

4. Systemic Juvenile Idiopathic Arthritis (SJIA). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following criteria (i and ii):

i. Patient meets ONE of the following conditions (a, b, or c):

a) Patient has tried one other systemic agent for this condition; OR

F) Note: Examples of one other systemic agent include a corticosteroid (oral, intravenous); a conventional synthetic disease-modifying antirheumatic drug (DMARD; e.g., methotrexate, leflunomide, sulfasalazine); or a 1-month trial of a nonsteroidal anti-inflammatory drug (NSAID). A previous trial of one biologic other than the requested drug (e.g., Actemra [tocilizumab intravenous injection, tocilizumab subcutaneous injection], a tumor necrosis factor inhibitor (e.g., an etanercept product [Enbrel, biosimilars]), an adalimumab product [Humira, biosimilars], or an infliximab product [Remicade, biosimilars], or Ilaris (canakinumab subcutaneous injection) also counts towards a trial of one other systemic agent for SJIA. A biosimilar of the requested biologic does not count.

b) Patient has at least moderate to severe active systemic features of this condition OR the patient has active systemic features with an active joint count of one joint or greater, according to the prescriber; OR

G) Note: Examples of moderate to severe active systemic features include fever, rash, lymphadenopathy, hepatomegaly, splenomegaly, and serositis.

c) Patient has active systemic features with concerns of progression to macrophage activation syndrome (MAS), as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Kineret. Approve for 1 year if the patient meets BOTH of the following (i and ii):

v. Patient has been established on this medication for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

vi. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

H)

5. Still's Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following criteria (i and ii):

i. Patient meets ONE of the following conditions (a, b, or c):

a) Patient meets ALL of the following criteria [(1) and (2)]:

(1) Patient has tried one corticosteroid; AND

(2) Patient has had an inadequate response to one conventional synthetic disease-modifying antirheumatic drug (DMARD) such as methotrexate given for at least 2 months or was intolerant to a conventional synthetic DMARD; OR

I) Note: A previous trial of one biologic (e.g., Actemra [tocilizumab intravenous injection, tocilizumab subcutaneous injection], Arcalyst [rilonacept subcutaneous injection], Ilaris [canakinumab subcutaneous injection]) other than the requested drug also counts towards a trial of one other systemic agent for Still's disease. A biosimilar of the requested biologic does not count.

b) Patient has at least moderate to severe active systemic features of this condition, according to the prescriber; OR

J) Note: Examples of moderate to severe active systemic features include fever, rash, lymphadenopathy, hepatomegaly, splenomegaly, and serositis.

c) Patient has active systemic features with concerns of progression to macrophage activation syndrome, as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a rheumatologist; OR

B) Patient is Currently Receiving Kineret. Approve for 1 year if the patient meets BOTH of the following (i and ii):

viii. Patient has been established on this medication for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

ix. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR

Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kineret is not recommended in the following situations:

1. **Ankylosing Spondylitis.** Kineret has been beneficial in a few patients with ankylosing spondylitis, but results are not consistent.[15,16] In a small open-label study, patients with active ankylosing spondylitis who were refractory to NSAIDs (n = 20) received Kineret 100 mg daily.[16] The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score decreased over a 6-month period but was not significant (5.8 at baseline vs. 5.0 at Week 12, and 4.8 at Week 24). No significant change was found in Bath Ankylosing Spondylitis Functional Index (BASFI), patients' and physicians' global assessment of general pain during the study. After 12 weeks, both the assessment in ankylosing spondylitis (ASAS) 20 and 40 responses improved in 10.5% of patients (intention-to-treat analysis). After 24 weeks, ASAS 20 was attained in 26% of patients, ASAS 40 in 21% of patients, and ASAS 70 in 10.5% of patients. Guidelines for axial spondyloarthritis from the Assessment of SpondyloArthritis International Society (ASAS)/European Union Against Rheumatism (EULAR) [2016] do not mention Kineret as a treatment option.[17]

2. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Data are lacking evaluating concomitant use of Kineret in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (See Appendix for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMRADs has a potential for a higher rate of adverse effects and lack controlled trial data in support of additive efficacy.[18]
   Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Kineret.

K)

5. **Lupus Arthritis.** The effectiveness and safety of Kineret were evaluated in an open 3-month pilot trial in patients (n = 4) with systemic lupus erythematosus (SLE) and severe, therapy-refractory non-erosive polyarthritis (three patients had deforming Jaccoud's arthropathy) and no other uncontrolled major organ involvement.[19] Patients were refractory to NSAIDs, antimalarials, corticosteroids, methotrexate, cyclophosphamide, and azathioprine. SLE was controlled with stable doses of corticosteroids and/or antirheumatic or immunosuppressive agents; pain was managed with NSAIDs and/or other medications. Patients had improved clinically after 4 weeks on Kineret, but after 12 weeks the clinical activity parameters tended to increase

again. The results from this study are preliminary and a larger controlled study is needed.

L)

6. **Osteoarthritis.** In a Phase II study in patients with painful osteoarthritis of the knee, Kineret 150 mg administered by intraarticular injection was well tolerated.[20] The study was not designed to assess the analgesic efficacy of Kineret. Patients with osteoarthritis of the knee were enrolled in a multicenter, double-blind, placebo-controlled study and randomized to Kineret 50 mg, Kineret 150 mg, or placebo for intraarticular injection.[21] Although the injections were well tolerated, there were no significant differences in improvement in knee pain, stiffness, function or cartilage turnover between Kineret doses and placebo. Similar to other studies in this population, there was a significant placebo effect noted.

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

[*] Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; [^] Off-label use of Kineret in JIA supported in guidelines; DMARDs – Disease-modifying antirheumatic drug.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Litfulo Prior Authorization Policy
- Litfulo™ (ritlecitinib capsules – Pfizer)

REVIEW DATE: 07/05/2023; selected revision: 07/26/2023

OVERVIEW

Litfulo, a kinase inhibitor, is indicated for the treatment of **severe alopecia areata** in patients ≥ 12 years of age.[1] It inhibits the janus kinase 3 (JAK) and tyrosine kinase expressed in hepatocellular carcinoma (TEC) pathways.

Guidelines

Although specific drugs are not mentioned, JAK inhibitors (JAKis) as a therapeutic class are addressed in an international expert opinion on treatments for alopecia areata (2020).[2] JAKis are identified among the therapies for treatment of extensive hair loss. First-line treatments for adults include topical and/or systemic corticosteroids. Steroid-sparing therapies to mitigate the risk associated with prolonged use of corticosteroids include cyclosporine, methotrexate, azathioprine, and JAKis. Based on the expert opinion, JAKis are considered the ideal option amongst systemic, steroid-sparing agents.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Litfulo. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Litfulo as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Litfulo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Litfulo is recommended in those who meet the following criteria:

FDA-Approved Indication

47. Alopecia Areata. Approve for the duration noted if the patient meets one of the following (A or B):
Note: Alopecia universalis and alopecia totalis are subtypes of alopecia areata.

A) Initial Therapy. Approve for 6 months if the patient meets all of the following (i, ii, iii, iv, and v):
- **i.** Patient is ≥ 12 years of age; AND
- **ii.** Patient has a current episode of alopecia areata lasting for ≥ 6 months; AND
- **iii.** Patient has ≥ 50% scalp hair loss; AND
- **iv.** Patient has tried at least one of the following for alopecia areata (a or b):
  - **a)** Conventional systemic therapy; OR
    Note: Examples of conventional systemic therapies include corticosteroids, methotrexate, and cyclosporine. An exception to the requirement for a trial of one conventional systemic agent can be made if the patient has already tried Olumiant (baricitinib tablet).

b) Topical corticosteroid; AND

v. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Litfulo. Approve for 1 year if the patient meets all of the following (i, ii, iii, and iv):

i. Patient is ≥ 12 years of age; AND

ii. Patient has been established on Litfulo for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).

iii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating Litfulo) in extent and density of scalp hair loss; AND

iv. According to the prescriber, the patient continues to require systemic therapy for treatment of alopecia areata.
Note: International consensus states that systemic treatment is best discontinued once complete regrowth has been achieved and maintained for 6 months or when regrowth is sufficient to be managed topically.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Litfulo is not recommended in the following situations:

105. Concurrent Use with an Oral or Topical Janus Kinase Inhibitor (JAKi).[1]
Litfulo should not be administered in combination with another JAKi. Combination therapy is generally not recommended due to a potential for a higher rate of adverse effects and lack of evidence for additive efficacy.
Note: Examples include Olumiant (baricitinib tablets), Rinvoq (upadacitinib tablets), Xeljanz (tofacitinib tablets), and Opzelura (ruxolitinib cream).

106. Concurrent Use with a Biologic Immunomodulator. Litfulo is not recommended in combination with biologic immunomodulators.[1]
Note: Examples include Adbry (tralokinumab-ldrm subcutaneous injection), Cinqair (reslizumab intravenous), Dupixent (dupilumab subcutaneous injection), Fasenra (benralizumab subcutaneous injection), Nucala (mepolizumab subcutaneous injection), Tezspire (tezepelumab-ekko subcutaneous injection), and Xolair (omalizumab subcutaneous injection).

107. Concurrent Use with Other Potent Immunosuppressants (e.g., cyclosporine, azathioprine).[1] Co-administration with other potent immunosuppressive drugs has the risk of added immunosuppression and has not been evaluated.

108. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

52. Litfulo® capsules [prescribing information]. New York, NY: Pfizer; June 2023.
53. Meah N, Wall D, York K, et al. The Alopecia Areata Consensus of Experts (ACE) study: Results of an international expert opinion on treatments for alopecia areata. *J Am Acad Dermatol*. 2020;83:123-30.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Olumiant Prior Authorization Policy
- Olumiant® (baricitinib tablets – Lilly)

REVIEW DATE: 06/28/2023; selected revision: 07/26/2023

OVERVIEW

Olumiant, an inhibitor of the Janus kinases (JAK) pathways, is indicated for the following uses:[1]

- **Alopecia Areata,** in adults with severe disease.
- **Coronavirus Disease 2019 (COVID-19)**, for hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). For COVID-19, the dose is 4 mg once daily for 14 days or until hospital discharge, whichever comes first.
- **Rheumatoid Arthritis**, in adults with moderate to severe active disease who have had an inadequate response to one or more tumor necrosis factor inhibitors. Olumiant is not recommended for use in combination with other JAK inhibitors, or in combination with biologics or potent immunosuppressants such as azathioprine or cyclosporine.

Guidelines

Olumiant is addressed in the following guidelines:

- **Alopecia Areata:** An international expert opinion on treatments for alopecia areata (2020) lists JAK inhibitors among the therapies for treatment of extensive hair loss. First-line treatments for adults include topical and/or systemic corticosteroids. Steroid-sparing therapies to mitigate the risk associated with prolonged use of corticosteroids include cyclosporine, methotrexate, and azathioprine.
- **COVID-19:** The Infectious Diseases Society of America (IDSA) and the National Institutes of Health (NIH) have developed treatment guidelines for the management of COVID-19; both guidelines address the use of Olumiant.[3,4] Both the IDSA and NIH guidelines recommend Olumiant for hospitalized patients with COVID-19 for a duration of 14 days or until discharge from the hospital.
- **Rheumatoid Arthritis:** Guidelines from the American College of Rheumatology (2021) recommend addition of a biologic or a targeted synthetic disease-modifying antirheumatic drug (DMARD) for a patient taking the maximum tolerated dose of methotrexate who is not at target.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Olumiant. Because of the specialized skills required for evaluation and diagnosis of patients treated with Olumiant as well as the monitoring required for adverse events and long-term efficacy, initial approval for certain indications requires Olumiant to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

109. All requests for use of Olumiant in a hospitalized patient with COVID-19 will be forwarded to the Medical Director. Of note, this includes requests for cytokine release syndrome associated with COVID-19.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Olumiant is recommended in those who meet one of the following criteria:

FDA-Approved Indications

48. Alopecia Areata. Approve for the duration noted if the patient meets one of the following (A or B):
Note: Alopecia universalis and alopecia totalis are subtypes of alopecia areata.
C) Initial Therapy. Approve for 6 months if the patient meets all of the following (i, ii, iii, iv, and v):
i. Patient is ≥ 18 years of age; AND
ii. Patient has a current episode of alopecia areata lasting for ≥ 6 months; AND
iii. Patient has ≥ 50% scalp hair loss; AND
iv. Patient has tried at least one of the following for alopecia areata (a or b):
a) Conventional systemic therapy; OR
Note: Examples of conventional systemic therapies include corticosteroids, methotrexate, and cyclosporine. An exception to the requirement for a trial of one conventional systemic agent can be made if the patient has already tried Litfulo (ritlecitinib capsules).
b) Topical corticosteroid; AND
v. The medication is prescribed by or in consultation with a dermatologist.
D) Patient is Currently Receiving Olumiant. Approve for 1 year if the patient meets all of the following (i, ii, iii, and iv):
i. Patient is ≥ 18 years of age; AND
ii. Patient has been established on the requested drug for at least 6 months; AND
ii. Note: A patient who has received < 6 months of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).
iii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating Olumiant) in extent and density of scalp hair loss; AND
iv. According to the prescriber, the patient continues to require systemic therapy for treatment of alopecia areata.
iii. Note: International consensus states that systemic treatment is best discontinued once complete regrowth has been achieved and maintained for 6 months or when regrowth is sufficient to be managed topically.

iv.

49. COVID-19 (Coronavirus Disease 2019) – Hospitalized Patient. For a patient who is hospitalized, forward all requests to the Medical Director. For a non-hospitalized patient, do not approve (refer to Conditions Not Recommended for Approval – COVID-19 – Non-Hospitalized Patient). Olumiant is indicated for COVID-19 only in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[1] For COVID-19, the dose is 4 mg once daily for 14 days or until hospital discharge, whichever comes first.
Note: This includes requests for cytokine release syndrome in a patient hospitalized with COVID-19.[3,4]

50. Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 6 months if the patient meets all of the following (i, ii, and iii):
i. Patient is ≥ 18 years of age; AND
ii. Patient meets ONE of the following (a or b):
a) Patient has had a 3-month trial of at least ONE tumor necrosis factor inhibitor; OR

b) Patient has tried at least one tumor necrosis factor inhibitor but was unable to tolerate a 3-month trial; AND

Note: Refer to Appendix for examples of tumor necrosis factor inhibitors used for rheumatoid arthritis. Conventional synthetic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine do not count.

iii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Olumiant. Approve for 1 year if the patient meets BOTH of the following (i and ii):

v. Patient has been established on the requested drug for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).

vi. Patient meets ONE of the following (a or b):

a) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR

Note: Examples of standardized and validated objective measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).

b) Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Olumiant is not recommended in the following situations:

110. Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD). Olumiant should not be administered in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see Appendix for examples).[1] Combination therapy is generally not recommended due to a potential for a higher rate of adverse effects and lack of evidence for additive efficacy.

Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Olumiant.

111. Concurrent Use with a Biologic Immunomodulator. Olumiant is not recommended in combination with biologic immunomodulators.[1]

Note: Examples include Adbry (tralokinumab-ldrm subcutaneous injection), Cinqair (reslizumab intravenous), Dupixent (dupilumab subcutaneous injection), Fasenra (benralizumab subcutaneous injection), Nucala (mepolizumab subcutaneous injection), Tezspire (tezepelumab-ekko subcutaneous injection), and Xolair (omalizumab subcutaneous injection).

112. Concurrent Use with Topical Janus Kinase Inhibitors (JAKis). Olumiant should not be administered in combination with a topical JAKi [e.g. Opzelura (ruxolitinib) cream)] used for Atopic Dermatitis. Combination therapy is generally not recommended due to a potential for a higher rate of adverse effects and lack of evidence for additive efficacy.

113. Concurrent use with Other Potent Immunosuppressants (e.g., azathioprine, cyclosporine).[1] Co-administration with other potent immunosuppressive drugs has the risk of added immunosuppression

and has not been evaluated in rheumatoid arthritis. Note: This does NOT exclude use of Olumiant with methotrexate; Olumiant has been evaluated with background methotrexate or in combinations with conventional synthetic DMARDs containing methotrexate.

114. COVID-19 (Coronavirus Disease 2019) – Non-Hospitalized Patient. Olumiant is only indicated in hospitalized adults with COVID requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[1] For COVID-19, the dose is 4 mg once daily for 14 days or until hospital discharge, whichever comes first.

115. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

54. Olumiant® tablets [prescribing information]. Indianapolis, IN: Lilly; June 2022.
55. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol*. 2021;73(7):1108-1123.
56. COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health. Available at: https://www.covid19treatmentguidelines.nih.gov/. Accessed on June 20, 2023.
57. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the treatment and management of patients with COVID-19. May 15, 2023. Available at: https://www.idsociety.org/COVID19guidelines. Accessed June 20, 2023.

APPENDIX

[*] Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Omvoh Intravenous Prior Authorization Policy
- Omvoh® (mirikizumab-mrkz intravenous infusion – Eli Lilly)

REVIEW DATE: 11/08/2023

OVERVIEW

Omvoh intravenous, a monoclonal antibody against the p19 subunit of the interleukin (IL)-23 cytokine, is indicated for **induction treatment of ulcerative colitis** (UC), in adults with moderate to severe active disease.[1]

In UC, a three-dose induction regimen (300 mg at Weeks 0, 4, and 8) is administered by IV infusion.[1] Following induction therapy with the IV product, the recommended maintenance is Omvoh subcutaneous injection, given as a 200 mg subcutaneous injection administered at Week 12 (4 weeks following the last induction dose), then once every 4 weeks thereafter.

- **Guidelines**

Current guidelines do not address the use of Omvoh for UC. The American Gastroenterological Association (2020) and the American College of Gastroenterology (2019) have clinical practice guidelines on the management of moderate to severe UC and make recommendations for the use of biologics for induction and maintenance of remission in adults.[2,3] Generally TNF inhibitors, Entyvio® (vedolizumab intravenous infusion/subcutaneous injection), Stelara® (ustekinumab intravenous infusion/subcutaneous injection), or Xeljanz®/Xeljanz® XR (tofacitinib tablets, tofacitinib extended-release tablets) are recommended for induction treatment of moderate to severe disease (strong recommendations, moderate quality of evidence). The guidelines also recommend that any drug that effectively treats induction should be continued for maintenance.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Omvoh intravenous. Because of the specialized skills required for evaluation and diagnosis of patients treated with Omvoh intravenous as well as the monitoring required for adverse events and long-term efficacy, approval requires Omvoh intravenous to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for three months, which is an adequate duration for the patient to receive three doses.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Omvoh intravenous is recommended in those who meet one of the following:

FDA-Approved Indication

1. **Ulcerative Colitis.** Approve three doses for induction if the patient meets the following (A, B, C, and D):
    - **A)** Patient is ≥ 18 years of age; AND
    - **B)** The medication will be used as induction therapy; AND
    - **C)** Patient meets ONE of the following (i or ii):
    - **i.** Patient has tried one systemic therapy; OR
      Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone or methylprednisolone. A trial of a mesalamine product does not count as a systemic therapy for ulcerative colitis. A trial of one biologic other than the requested medication also counts as a trial of one systemic agent for ulcerative colitis. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for ulcerative colitis.
    - **ii.** Patient meets BOTH of the following (a and b):
        - **a)** Patient has pouchitis; AND
        - **b)** Patient has tried an antibiotic, probiotic, corticosteroid enema, or mesalamine enema; AND
          Note: Examples of antibiotics include metronidazole and ciprofloxacin. Examples of corticosteroid enemas include hydrocortisone enema.
        - **D)** The medication is prescribed by or in consultation with a gastroenterologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Omvoh intravenous is not recommended in the following situations:

3. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Omvoh intravenous should not be administered in combination with another biologic or with a targeted synthetic DMARD for an inflammatory condition (see Appendix for examples). Data are lacking evaluating concomitant use of Omvoh with another biologic or with a targeted synthetic DMARD for an inflammatory condition (see Appendix for examples). Combination therapy is generally not recommended due to a potential for a higher rate of adverse effects and lack of controlled data supporting additive efficacy. Note: This does NOT exclude the use of conventional agents (e.g., methotrexate, 6-mercaptopurine, azathioprine, and sulfasalazine) in combination with Omvoh intravenous.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Omvoh injection [prescribing information]. Indianapolis, IN: Eli Lilly; October 2023.
2. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol.* 2019;114(3):384-413.
3. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterology*. 2020 Apr158(5):1450-1461.

APPENDIX

[*] Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Omvoh Subcutaneous Prior Authorization Policy
- Omvoh® (mirikizumab-mrkz subcutaneous injection – Eli Lilly)

REVIEW DATE: 11/08/2023

OVERVIEW

Omvoh subcutaneous injection, a monoclonal antibody against the p19 subunit of the interleukin (IL)-23 cytokine, is indicated for the **maintenance treatment of ulcerative colitis** (UC), in adults with moderate to severe active disease.[1]

In UC, a three-dose induction regimen (300 mg at Weeks 0, 4, and 8) is administered by IV infusion.[1] Following induction therapy with the IV product, the recommended maintenance is Omvoh subcutaneous injection, given as a 200 mg subcutaneous injection administered at Week 12 (4 weeks following the last induction dose), then once every 4 weeks thereafter.

- **Guidelines**

Current guidelines do not address the use of Omvoh for UC. The American Gastroenterological Association (2020) and the American College of Gastroenterology (2019) have clinical practice guidelines on the management of moderate to severe UC and make recommendations for the use of biologics for induction and maintenance of remission in adults.[2,3] Generally TNF inhibitors, Entyvio® (vedolizumab intravenous infusion/subcutaneous injection), Stelara® (ustekinumab intravenous infusion/subcutaneous injection), or Xeljanz®/Xeljanz® XR (tofacitinib tablets, tofacitinib extended-release tablets) are recommended for induction treatment of moderate to severe disease (strong recommendations, moderate quality of evidence). The guidelines also recommend that any drug that effectively treats induction should be continued for maintenance.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Omvoh subcutaneous. Because of the specialized skills required for evaluation and diagnosis of patients treated with Omvoh subcutaneous as well as the monitoring required for adverse events and long-term efficacy, approval requires Omvoh subcutaneous to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Omvoh subcutaneous is recommended in those who meet one of the following:

FDA-Approved Indication

15. Ulcerative Colitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. According to the prescriber, the patient will receive three induction doses with Omvoh intravenous within 3 months of initiating therapy with Omvoh subcutaneous; AND

iii. Patient meets ONE of the following (a or b):

a) Patient has had a trial of one systemic agent for ulcerative colitis; OR

Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone, methylprednisolone. A trial of a mesalamine product does not count as a systemic therapy for ulcerative colitis. A trial of one biologic other than the requested drug also counts as a trial of one systemic agent for ulcerative colitis. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for ulcerative colitis.

b) Patient meets BOTH of the following [(1) and (2)]:

(3) Patient has pourchitis; AND

(4) Patient has tried an antibiotic, probiotic, corticosteroid enema, or mesalamine enema; AND

Note: Examples of antibiotics include metronidazole and ciprofloxacin. Examples of corticosteroid enemas include hydrocortisone enema.

iv. The medication is prescribed by or in consultation with a gastroenterologist; OR

B) Patient is Currently Receiving Omvoh Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

vi. Patient has been established on the requested drug for at least 6 months; AND

4. Note: A patient who has received < 6 months of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).

vii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR

5. Note: Examples of assessment for inflammatory response include fecal markers (e.g., fecal calprotectin), serum markers (e.g., C-reactive protein), endoscopic assessment, and/or reduced dose of corticosteroids.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or decreased rectal bleeding.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Omvoh subcutaneous is not recommended in the following situations:

5. Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD). Omvoh should not be administered in combination with another biologic or with a targeted synthetic DMARD for an inflammatory condition (see Appendix for examples). Data are lacking evaluating concomitant use of Omvoh with another biologic or with a targeted synthetic DMARD for an inflammatory condition (see Appendix for examples). Combination therapy is generally not recommended due to a potential for a higher rate of adverse effects and lack of controlled data supporting additive efficacy. Note: This does NOT exclude the use of conventional agents (e.g., methotrexate, 6-mercaptopurine, azathioprine, and sulfasalazine) in combination with Omvoh.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

6. Omvoh injection [prescribing information]. Indianapolis, IN: Eli Lilly; October 2023.
7. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol.* 2019;114(3):384-413.
8. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterology*. 2020 Apr158(5):1450-1461.

APPENDIX

[*] Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

ii. PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Orencia Intravenous Prior Authorization Policy
- Orencia® (abatacept intravenous infusion – Bristol-Myers Squibb)

REVIEW DATE: 02/22/2023

OVERVIEW

Orencia intravenous, a selective T-cell costimulation modulator, is indicated for the following uses:

- **Graft-versus-host disease (GVHD)**, for prophylaxis of acute GVHD in combination with a calcineurin inhibitor and methotrexate, in patients ≥ 2 years of age undergoing hematopoietic stem cell transplantation from a matched or 1 allele-mismatched unrelated donor.
- **Juvenile idiopathic arthritis**, in patients ≥ 2 years of age with moderately to severely active polyarticular disease.
- **Psoriatic arthritis (PsA)**, in adults with active disease.
- **Rheumatoid arthritis**, in adults with moderately to severely active disease.

Orencia is not recommended for use concomitantly with other potent immunosuppressants such as biologics or Janus kinase inhibitors. Orencia is available as an intravenous infusion that is dosed on body weight. There is also a subcutaneous injection available in prefilled syringes. Some patients initiating therapy with Orencia subcutaneous will receive a single loading dose with Orencia intravenous.

Guidelines

Orencia is addressed in guidelines for treatment of various inflammatory conditions.

- **GVHD:** Guidelines for hematopoietic cell transplantation for pre-transplant recipient evaluation and management of GVHD are available from the National Comprehensive Cancer Network (NCCN) [version 3.2022 – January 24, 2023].[9] Immunosuppresive agents are commonly used for the prevention of GVHD. Orencia is among the therapies listed for treatment of steroid-refractory chronic GVHD.
- **Juvenile Idiopathic Arthritis:** Guidelines from American College of Rheumatology (ACR) [2019] list biologics among the treatment options for subsequent therapy in patients with polyarthritis.[3] Initial therapy with a biologic may be considered for patients with risk factors and involvement of high-risk joints (e.g., cervical spine, wrist, or hip), high disease activity, and/or those judged to be at high risk of disabling joint damage. In patients with active sacroiliitis or enthesitis despite nonsteroidal anti-inflammatory drug use, a tumor necrosis factor inhibitor (TNFi) is recommended.
- **PsA:** Guidelines from ACR (2018) recommend TNFis over other biologics for use in treatment-naïve patients with PsA and in those who were previously treated with an oral therapy.[4] However, Orencia may be considered over other biologics in patients with recurrent or serious infections.
- **Rheumatoid Arthritis:** Guidelines from the ACR (2021) recommend addition of a biologic or a targeted synthetic disease modifying anti-rheumatic drug (DMARD) for a patient taking the maximum tolerated dose of methotrexate who is not at target.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Orencia intravenous. Because of the specialized skills required for evaluation and diagnosis of patients treated with Orencia as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Orencia

intravenous to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. For prevention of GVHD, the approval duration is for 30 days, which is an adequate duration for the patient to receive four doses.

2.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Orencia intravenous is recommended in those who meet one of the following criteria:

FDA-Approved Indications

3. Graft-Versus-Host Disease – Prevention. Approve for 4 doses if the patient meets ALL of the following (A, B, C, D, E, and F):

a) Patient is ≥ 2 years of age; AND

b) Orencia is being used for prevention of acute graft-versus-host disease; AND

c) Patient will also receive a calcineurin inhibitor for prevention of acute graft-versus-host disease; AND

4. Note: Examples of calcineurin inhibitors include cyclosporine and tacrolimus.

a) Patient will also receive methotrexate for prevention of acute graft-versus-host disease; AND

b) Patient will undergo hematopoietic stem cell transplantation from one of the following donors (i or ii):

i. Matched unrelated donor; OR

ii. 1-allele-mismatched unrelated donor; AND

c) The medication is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center.

5. Juvenile Idiopathic Arthritis (JIA). Approve for the duration noted if the patient meets ONE of the following (A or B):

Note: This includes JIA regardless of type of onset. JIA is also referred to as Juvenile Rheumatoid Arthritis.

a) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following criteria (i and ii):

i. Patient meets one of the following (a, b, c, or d):

a) Patient has tried one other agent for this condition; OR

NNN) Note: Examples of therapies which could have been tried include methotrexate, sulfasalazine, leflunomide, and a nonsteroidal anti-inflammatory drug (NSAID). A biologic other than the requested drug also counts as a trial of one agent for JIA. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for JIA.

b) Patient will be starting on therapy concurrently with methotrexate, sulfasalazine, or leflunomide; OR

c) Patient has an absolute contraindication to methotrexate, sulfasalazine, or leflunomide; OR

OOO) Note: Examples of absolute contraindications to methotrexate include pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, blood dyscrasias.

d) Patient has aggressive disease, as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a rheumatologist.

b) Patient is Currently Receiving Orencia (Intravenous or Subcutaneous). Approve for 1 year if the patient meets BOTH of the following (i and ii):

ii. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include Physician Global Assessment (MD global), Parent/Patient Global Assessment of Overall Well-Being (PGA), Parent/Patient Global Assessment of Disease Activity (PDA), Juvenile Arthritis Disease Activity Score (JDAS), Clinical Juvenile Arthritis Disease Activity Score (cJDAS), Juvenile Spondyloarthritis Disease Activity Index (JSpADA), serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

d) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as improvement in limitation of motion, less joint pain or tenderness, decreased duration of morning stiffness or fatigue, improved function or activities of daily living.

6. Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

a) Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist or a dermatologist.

b) Patient is Currently Receiving Orencia (Intravenous or Subcutaneous). Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requesting drug); OR

7. Note: Examples of standardized measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsA DAS), Grace Index, Leeds Enthesitis Score (LEI), Spondyloarthritis Consortuium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths).

8. Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

a) Initial Therapy. Approve for 6 months if the patient meets the following (i and ii):

i. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND
Note: Examples of conventional synthetic DMARDs include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already had a 3-month trial of at least one biologic other than the requested drug. A biosimilar of the requested

biologic does not count. Refer to Appendix for examples of biologics used for rheumatoid arthritis. A patient who has already tried a biologic is not required to "step back" and try a conventional synthetic DMARD.

ii. The medication is prescribed by or in consultation with a rheumatologist.

b) Patient is Currently Receiving Orencia (Intravenous or Subcutaneous). Approve for 1 year if the patient meets BOTH of the following (i and ii):

ix. Patient has been established on therapy for at least 6 months; AND

9. Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR

Note: Examples of standardized and validated measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).

b) Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

PPP)

QQQ)

RRR) CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Orencia intravenous is not recommended in the following situations:

1. **Ankylosing Spondylitis.** In an open-label Phase II trial, Orencia was administered intravenously on Days 1, 15, 29, and every 28 days thereafter to patients with active ankylosing spondylitis.[5] Patients received a fixed dosage of Orencia of approximately 10 mg/kg based on body weight. The primary endpoint was a 40% improvement in disease activity at Week 24 in the Assessment of SpondyloArthritis international Society criteria (ASAS 40). At Week 24, the ASAS 40 was 13.3% (n = 2/15) in tumor necrosis factor inhibitor (TNFi)-naïve patients compared with no responses in patients who had previously failed TNFis (n = 15). ASAS 20 response was 26.7% (n = 4/15) in TNFi-naïve patients compared with 20% (n = 3/15) in those who had previously failed TNFis. A major response was not shown with treatment to Orencia.

2. **Concurrent Use with a Biologic or with a Targeted Synthetic DMARD.** Orencia intravenous should not be administered in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see Appendix for examples).[1] Combination therapy is generally not recommended due to a higher rate of adverse events with combinations and lack of data supportive of additional efficacy. Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Orencia intravenous.

3. **Inflammatory Bowel Disease (i.e., Crohn's Disease, Ulcerative Colitis).** In placebo-controlled trials evaluating the efficacy of Orencia intravenous for induction and maintenance in adults with active, moderate to severe Crohn's disease (n = 451) and ulcerative colitis (n = 490), Orencia was no more effective than placebo.[6] Patients were randomized to Orencia 30, 10, or 3 mg/kg (according to body weight) or placebo and dosed at Weeks 0, 2, 4, and 8. A total of 90 patients with Crohn's disease and 131 patients with ulcerative colitis who responded to induction were then randomized to Orencia 10 mg/kg or placebo every 4 weeks through Week 52. When used for induction of Crohn's disease, 17.2%,

10.2%, and 15.5% of patients receiving Orencia 30 mg, 10 mg, and 3 mg/kg achieved a clinical response at Weeks 8 and 12 compared with 14.4% of patients receiving placebo (P = not significant [NS] for all comparisons). In patients with Crohn's disease, response and remission at Week 52 was not significantly different between the Orencia intravenous and placebo treatment groups. When used as induction therapy in ulcerative colitis, 21.4%, 19.0%, and 20.3% of patients receiving Orencia 30 mg, 10 mg, and 3 mg/kg achieved a clinical response at Week 12 compared with 29.5% of patients receiving placebo (P = 0.043 for 10 mg/kg vs. placebo; other comparisons P = NS). At Week 52, 12.5% (n = 8/64) and 14.1% (n = 9/64) of patients with ulcerative colitis were in remission (P = NS) and 17.2% of patients in each treatment group (n = 11/64 for each group) had achieved a response.

4. **Psoriasis**. (Note: Patients with concomitant plaque psoriasis and psoriatic arthritis may be reviewed under the psoriatic arthritis criteria above.) In the pivotal trial evaluating Orencia subcutaneous for psoriatic arthritis, there was not a significant difference at Week 24 in the proportion of patients with a 50% reduction in the Psoriasis Area and Severity Index (PASI 50) response vs. placebo ± conventional synthetic (cs)DMARD (27% vs. 20% with placebo ± csDMARD; P = NS).[8] In a multicenter, Phase I, 26-week, open-label dose-escalation study, 43 patients with stable plaque psoriasis (10% to 49% body surface area involvement) received four doses of Orencia given as a 1-hour intravenous infusion on Days 1, 3, 16, and 29.[7] The starting dose was 0.5 mg/kg. Four to six patients were accrued to each of eight dose levels: 0.5, 1, 2, 4, 8, 16, 25, and 50 mg/kg. A parallel control group was matched for age and overall disease severity. In all, 46% of patients on Orencia achieved a 50% or greater sustained improvement in clinical disease activity (Physician's Global Assessment of disease activity) compared with baseline psoriasis evaluation. Progressively greater effects were observed with the highest doses. Further studies are needed to establish safety and efficacy, as well as appropriate dosing in plaque psoriasis.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Orencia® intravenous infusion [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; June 2020.
2. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol*. 2021;73(7):1108-1123.
3. Ringold S, Angeles-Han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for non-systemic polyarthritis, sacroiliitis, and enthesitis. *Arthritis Rheumatol*. 2019;71(6):717-734.
4. Singh JA, Guyatt G, Ogdie A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the treatment of psoriatic arthritis. *Arthritis Care Res (Hoboken)*. 2019;71(1):2-29.
5. Song IH, Heldmann F, Rudwaleit M, et al. Treatment of active ankylosing spondylitis with abatacept: an open-label, 24-week pilot study. *Ann Rheum Dis*. 2011;70(6):1108-1110.
6. Sandborn WJ, Colombel JF, Sands BE, et al. Abatacept for Crohn's disease and ulcerative colitis. *Gastroenterology*. 2012;143(1):62-69.
7. Abrams JR, Lebwohl MG, Guzzo CA, et al. CTLA4Ig-mediated blockade of T-cell costimulation in patients with psoriasis vulgaris. *J Clin Invest*. 1999;103:1243-1252.
8. Mease PJ, Gottlieb AB, van der Heijde D, et al. Efficacy and safety of abatacept, a T-cell modulator, in a randomised, double-blind, placebo-controlled, phase III study in psoriatic arthritis. *Ann Rheum Dis*. 2017;76(9):1550-1558.
9. The NCCN Hematopoietic Cell Transplantation (HCT) Clinical Practice Guidelines in Oncology (version 3.2022 – January 24, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 1, 2023.

APPENDIX

[*] Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Orencia Subcutaneous Prior Authorization Policy
- Orencia® (abatacept subcutaneous injection – Bristol Myers Squibb)

REVIEW DATE: 08/23/2023

OVERVIEW

Orencia subcutaneous, a selective T-cell costimulation modulator, is indicated for the following uses:[1]

- **Rheumatoid arthritis**, in adults with moderately to severely active disease.
- **Juvenile idiopathic arthritis**, in patients ≥ 2 years of age with moderately to severely active polyarticular disease.
- **Psoriatic arthritis**, in adults with active disease.

Per the product labeling, Orencia is not recommended for use concomitantly with other potent immunosuppressants such as biologics or Janus kinase inhibitors.

Guidelines

Orencia is addressed in guidelines for treatment of various inflammatory conditions.

- **Rheumatoid Arthritis:** Guidelines from the American College of Rheumatology (ACR) [2021] recommend addition of a biologic or a targeted synthetic disease-modifying antirheumatic drug (DMARD) for a patient taking the maximum tolerated dose of methotrexate who is not at target.[2]
- **Juvenile Idiopathic Arthritis:** Guidelines from ACR (2019) list biologics among the treatment options for subsequent therapy in patients with polyarthritis.[3] Initial therapy with a biologic may be considered for patients with risk factors and involvement of high-risk joints (e.g., cervical spine, wrist, or hip), high disease activity, and/or those judged to be at high risk of disabling joint damage. In patients with active sacroiliitis or enthesitis despite a nonsteroidal anti-inflammatory drug, a tumor necrosis factor inhibitor (TNFi) is recommended.
- **Psoriatic Arthritis:** Guidelines from ACR (2018) recommend TNFis over other biologics for use in treatment-naïve patients with psoriatic arthritis and in those who were previously treated with an oral therapy.[4] However, Orencia may be considered over other biologics in patients with recurrent or serious infections.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Orencia subcutaneous injection. Because of the specialized skills required for evaluation and diagnosis of patients treated with Orencia as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Orencia subcutaneous to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Orencia subcutaneous is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Rheumatoid Arthritis.** Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND

Note: Examples of conventional synthetic DMARDs include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already has a 3-month trial at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for rheumatoid arthritis. A patient who has already tried a biologic is not required to "step back" and try a conventional synthetic DMARD.

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Orencia (Intravenous or Subcutaneous). Approve for 1 year if the patient meets BOTH of the following (i and ii):

x. Patient has been established on therapy for at least 6 months; AND

2. Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

iii. Patient meets at least one of the following (a or b):

b) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR

Note: Examples of objective measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate or C-reactive protein, Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).

b) Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

3. **Juvenile Idiopathic Arthritis (JIA).** Approve for the duration noted if the patient meets ONE of the following (A or B):

vii. Note: This includes JIA regardless of type of onset. JIA is also referred to as Juvenile Rheumatoid Arthritis.

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

iii. Patient meets one of the following (a, b, c, or d):

m) Patient has tried one other agent for this condition; OR

xi. Note: Examples of therapies which could have been tried include methotrexate, sulfasalazine, leflunomide, or a nonsteroidal anti-inflammatory drug (NSAID). A previous trial of one biologic other than the requested drug also counts as a trial of one agent for JIA. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for JIA.

n) Patient will be starting on therapy concurrently with methotrexate, sulfasalazine, or leflunomide; OR

o) Patient has an absolute contraindication to methotrexate, sulfasalazine, or leflunomide; OR

xii. Note: Examples of absolute contraindications to methotrexate include pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, or blood dyscrasias.

p) Patient has aggressive disease, as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a rheumatologist.

C) Patient is Currently Receiving Orencia (Intravenous or Subcutaneous). Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include Physician Global Assessment (MD global), Parent/Patient Global Assessment of Overall Well-Being (PGA), Parent/Patient Global Assessment of Disease Activity (PDA), Juvenile Arthritis Disease Activity Score (JDAS), Clinical Juvenile Arthritis Disease Activity Score (cJDAS), Juvenile Spondyloarthritis Disease Activity Index (JSpADA), serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

e) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as improvement in limitation of motion, less joint pain or tenderness, decreased duration of morning stiffness or fatigue, improved function or activities of daily living.

4. Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving Orencia (Intravenous or Subcutaneous). Approve for 1 year if the patient meets BOTH of the following (i and ii):

xxxi. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

xxxii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requesting drug); OR
5. Note: Examples of objective measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsA DAS), Grace Index, Leeds Enthesitis Score (LEI), Spondyloarthritis Consortium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Orencia subcutaneous is not recommended in the following situations:

6. **Ankylosing Spondylitis.** In an open-label Phase II trial, Orencia was administered intravenously on Days 1, 15, 29, and every 28 days thereafter to patients with active ankylosing spondylitis.[5] Patients received a fixed dosage of Orencia of approximately 10 mg/kg based on body weight. The primary endpoint was a 40% improvement in disease activity at Week 24 in the Assessment of SpondyloArthritis international Society criteria (ASAS 40). At Week 24, the ASAS 40 was 13.3% (n = 2/15) in TNFi-naïve patients compared with no responses in patients who had previously failed TNFis (n = 15). ASAS 20 response was 26.7% (n = 4/15) in TNFi-naïve patients compared with 20% (n = 3/15) in those who had previously failed TNFis. A major response was not shown with Orencia treatment.

7. **Concurrent Use with a Biologic or with a Targeted Synthetic DMARD.** Orencia subcutaneous should not be administered in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see Appendix for examples).[1] Combination therapy is generally not recommended due to a higher rate of adverse events with combinations and lack of data supportive of additional efficacy.
   Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Orencia subcutaneous.

8. **Inflammatory Bowel Disease (i.e., Crohn's Disease, Ulcerative Colitis).** In placebo-controlled trials evaluating the efficacy of Orencia intravenous for induction and maintenance in adults with active, moderate to severe Crohn's disease (n = 451) and ulcerative colitis (n = 490), Orencia was no more effective than placebo.[6] Patients were randomized to Orencia 30 mg/kg, 10 mg/kg, or 3 mg/kg (according to body weight) or placebo and dosed at Weeks 0, 2, 4, and 8. A total of 90 patients with Crohn's disease and 131 patients with ulcerative colitis who responded to induction were then randomized to Orencia 10 mg/kg or placebo every 4 weeks through Week 52. When used for induction of Crohn's disease, 17.2%, 10.2%, and 15.5% of patients receiving Orencia 30 mg/kg, 10 mg/kg, and 3 mg/kg achieved a clinical response at Weeks 8 and 12 compared with 14.4% of patients receiving placebo (P = not significant [NS] for all comparisons). In patients with Crohn's disease, response and remission at Week 52 was not significantly different between the Orencia intravenous and placebo treatment groups. When used as induction therapy in ulcerative colitis, 21.4%, 19.0%, and 20.3% of patients receiving Orencia 30 mg, 10 mg, and 3 mg/kg achieved a clinical response at Week 12 compared with 29.5% of patients receiving placebo (P = 0.043 for 10 mg/kg vs. placebo; other comparisons P = NS). At Week 52, 12.5% (n = 8/64) and 14.1% (n = 9/64) of patients with ulcerative colitis were in remission (P = NS) and 17.2% of patients in each treatment group (n = 11/64 for each group) had achieved a response.

9. **Psoriasis**. In the pivotal trial evaluating Orencia subcutaneous for psoriatic arthritis, there was not a significant difference at Week 24 in the proportion of patients with a 50% reduction in the Psoriasis Area and Severity Index (PASI 50) response vs. placebo ± conventional synthetic DMARD (27% vs. 20% with placebo ± conventional synthetic DMARD; P = NS).[8] In a multicenter, Phase I, 26-week, open-label dose-escalation study, 43 patients with stable plaque psoriasis (10% to 49% body surface area involvement) received four doses of Orencia given as a 1-hour intravenous infusion on Days 1, 3, 16 and 29.[7] The starting dose was 0.5 mg/kg. Four to six patients were accrued to each of eight dose levels: 0.5, 1, 2, 4, 8, 16, 25 and 50 mg/kg. A parallel control group was matched for age and overall disease severity. In all, 46% of patients on Orencia achieved a 50% or greater sustained improvement in clinical disease activity (Physician's Global Assessment of disease activity) compared with baseline

psoriasis evaluation. Progressively greater effects were observed with the highest doses. Further studies are needed to establish safety and efficacy, as well as appropriate dosing, in plaque psoriasis. Note: Patients with concomitant plaque psoriasis and psoriatic arthritis may be reviewed under the psoriatic arthritis criteria above.

10. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Orencia® subcutaneous injection [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; October 2021.
2. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol*. 2021;73(7):1108-1123.
3. Ringold S, Angeles-Han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for non-systemic polyarthritis, sacroiliitis, and enthesitis. *Arthritis Rheumatol*. 2019;71(6):717-734.
4. Singh JA, Guyatt G, Ogdie A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the treatment of psoriatic arthritis. *Arthritis Care Res (Hoboken)*. 2019;71(1):2-29.
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8. Mease PJ, Gottlieb AB, van der Heijde D, et al. Efficacy and safety of abatacept, a T-cell modulator, in a randomised, double-blind, placebo-controlled, phase III study in psoriatic arthritis. *Ann Rheum Dis*. 2017;76(9):1550-1558.

APPENDIX

2. * Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Otezla Prior Authorization Policy
- Otezla® (apremilast tablets – Amgen)

REVIEW DATE: 06/07/2023

OVERVIEW

Otezla, an oral phosphodiesterase 4 (PDE4) inhibitor, is indicated for the following indications:[1]
- **Behcet's disease**, in adults with oral ulcers.
- **Plaque psoriasis**, in adults who are candidates for phototherapy or systemic therapy.
- **Psoriatic arthritis**, in adults with active disease.

Guidelines

Otezla is addressed in guidelines for treatment of inflammatory conditions.
- **Behcet's Disease:** Recommendations for the management of Behcet's disease from the European League Against Rheumatism (2018) mention Otezla as a treatment option for Behcet's disease with mucocutaneous involvement.[7] Other options include topical steroids, colchicine, azathioprine, thalidomide, interferon alpha, and tumor necrosis factor inhibitors (TNFis). TNFis are also listed among the therapeutic options for patients who present with eye involvement, refractory venous thrombosis, arterial involvement, refractory/severe gastrointestinal involvement, nervous system involvement, and/or joint involvement.
- **Plaque Psoriasis:** Joint guidelines from the American Academy of Dermatology and National Psoriasis Medical Board (2020) have been published for management of psoriasis with systemic non-biologic therapies.[8] These guidelines list Otezla as a monotherapy treatment option for patients with moderate to severe plaque psoriasis. For treatment of moderate to severe psoriasis in adults, Otezla has a similar level of evidence and strength of recommendation as methotrexate. Additionally, data support use of methotrexate in combination with other systemic therapies for psoriasis,[4,8] whereas there is no strong evidence supporting combination use of Otezla with other systemic therapies or with phototherapy.[4]
- **Psoriatic Arthritis:** Guidelines from the American College of Rheumatology (2019) recommend TNFis over other biologics and Otezla for use in treatment-naïve patients with psoriatic arthritis and in those who were previously treated with an oral therapy.[6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Otezla. Because of the specialized skills required for evaluation and diagnosis of patients treated with Otezla as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Otezla to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Otezla is recommended in those who meet one of the following criteria:

FDA-Approved Indications
i.

1. **Behcet's Disease.** Approve for the duration noted if the patient meets ONE of the following criteria (A or B):
   - **A)** Initial Therapy. Approve for 4 months if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has oral ulcers or other mucocutaneous involvement; AND
     - **iii.** Patient has tried at least ONE other systemic therapy; AND
       Note: Examples of systemic therapies include colchicine, systemic corticosteroids, azathioprine, thalidomide, interferon alpha, tumor necrosis factor inhibitors (e.g., an adalimumab product [Humira, biosimilars], an etanercept product [Enbrel, biosimilars], Cimzia [certolizumab pegol subcutaneous injection], Simponi [golimumab subcutaneous injection], Simponi Aria [golimumab intravenous infusion], or an infliximab product [Remicade, biosimilars]).
     - **iv.** The medication is prescribed by or in consultation with a rheumatologist or dermatologist.
   - **B)** Patient is Currently Receiving Otezla. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient has been established on therapy for at least 4 months; AND
       Note: A patient who has received < 4 months of therapy or who is restarting therapy should be considered under criterion A (Initial Therapy).
     - **ii.** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Otezla); AND
       Note: Examples of objective measures are dependent upon organ involvement but may include best-corrected visual acuity (if ophthalmic manifestations); serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate); ulcer depth, number, and/or lesion size.
     - **iii.** Compared with baseline (prior to initiating Otezla), patient experienced an improvement in at least one symptom, such as decreased pain, or improved visual acuity (if ophthalmic manifestations).

2. **Plaque Psoriasis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 4 months if the patient meets ALL of the following criteria (i, ii, and iii):
     - **i.** Patient is ≥18 years of age; AND
     - **ii.** Patient meets ONE of the following conditions (a or b):
       - **a)** Patient has tried at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR
         Note: Examples of traditional systemic agents for psoriasis include methotrexate, cyclosporine, acitretin tablets, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already had a 3-month trial or previous intolerance to at least one biologic. Refer to Appendix for examples of biologics used for plaque psoriasis. A patient who has already tried a biologic for psoriasis is not required to "step back" and try a traditional systemic agent for psoriasis.
       - **b)** Patient has a contraindication to methotrexate, as determined by the prescriber; AND
     - **iii.** The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Otezla. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

ii. Patient has been established on therapy for at least 4 months; AND
Note: A patient who has received < 4 months of therapy or who is restarting therapy with with the requested drug should be considered under criterion A (Initial Therapy).

iii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating the requested drug) in at least one of the following: estimated body surface area, erythema, induration/thickness, and/or scale of areas affected by psoriasis; AND

iv. Compared with baseline (prior to receiving the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain, itching, and/or burning.

3. Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of following (i and ii):

i. *Patient is ≥ 18 years of age; AND*

ii. The medication is prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving Otezla. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on the requested drug for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Otezla); OR
Note: Examples of standardized measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsA DAS), Grace Index, Leeds Enthesitis Score (LEI), Spondyloarthritis Consortuium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating Otezla), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Otezla is not recommended in the following situations:

11. Ankylosing Spondylitis. Current evidence does not support use of Otezla in ankylosing spondylitis. In a published, double-blind, placebo-controlled, Phase III study, patients (n = 490) were randomized in a 1:1:1 ratio to treatment with Otezla 30 mg twice daily, Otezla 20 mg twice daily, or placebo.[9] At Week 16, there was not a statistically significant change from baseline compared with placebo in the primary endpoint, which was the Assessment of the Spondyloarthritis international Society 20 (ASAS20) response.

12. Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARD). Otezla is a small molecule that specifically targets intracellular PDE4 and has an inhibitory effect on multiple cytokines involved in the inflammatory process, including tumor necrosis

factor, interferon gamma, interleukin (IL)-12, and IL-23.[2-3] Co-administration of Otezla with a biologic or another targeted synthetic DMARD (see Appendix for examples) has the risk of added immunosuppression and has not been adequately evaluated.
Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Otezla.

B)

13. **Rheumatoid Arthritis.** Current evidence does not support use of Otezla in rheumatoid arthritis. A multicenter, double-blind, Phase II study (n = 237) randomized patients in a 1:1:1 ratio to treatment with Otezla 20 mg twice daily, Otezla 30 mg twice daily, or placebo.[10] All patients were required to take a stable dose of methotrexate throughout the study. At Week 16, a similar proportion of patients in all treatment groups achieved an American College of Rheumatology (ACR) 20 response (28%, 34%, and 35%, respectively). At Week 16, patients who were non-responders, defined as patients with a swollen joint count and tender joint count that had not improved by at least 20%, were required to enter early escape (patients who were receiving placebo were transitioned to Otezla 20 mg twice daily and patients receiving Otezla continued on the assigned therapy for an additional year). At Week 24, all patients who received placebo were similarly transitioned to Otezla. At Weeks 24 and 52, both doses of Otezla were associated with generally similar changes versus placebo, including ACR 20, ACR 50, and ACR 70. A subset of patients underwent magnetic resonance imaging evaluation; however, no significant difference in response rate was observed at Week 16. The study was terminated early; data were not analyzed at Year 2 as originally planned.

14. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

[*] Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARDs – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Rinvoq Prior Authorization Policy
- Rinvoq® (upadacitinib extended-release tablets – AbbVie)

REVIEW DATE: 02/15/2023; selected revision 05/24/2023

OVERVIEW

Rinvoq, a Janus kinase inhibitor (JAKi), is indicated for the following uses:[1]

- **Ankylosing spondylitis**, for treatment of active disease in adults who have had an inadequate response or intolerance to one or more tumor necrosis factor inhibitors (TNFis).
- **Atopic dermatitis**, for treatment of refractory, moderate to severe atopic dermatitis in patients ≥ 12 years of age, whose disease is not adequately controlled with other systemic drug products (including biologics) or when those therapies are not advisable.
- **Crohn's disease**, for treatment of moderately to severely active disease in adults who have had an inadequate response or intolerance to one or more TNFis.
- **Non-radiographic axial spondyloarthritis**, in adults with objective signs of inflammation who have had an inadequate response or intolerance to one or more TNFis.
- **Psoriatic arthritis**, for treatment of active disease in adults who have had an inadequate response or intolerance to one or more TNFis.
- **Rheumatoid arthritis**, for treatment of moderately to severely active disease in adults who have had an inadequate response or intolerance to one or more TNFis.
- **Ulcerative colitis**, for treatment of moderately to severely active disease in adults who have had an inadequate response or intolerance to one or more TNFis.

A)

B) Rinvoq is not recommended for use in combination with other JAKis, biologics, or potent immunosuppressants such as azathioprine or cyclosporine.

Guidelines

Guidelines are available for treatment of inflammatory conditions:

- **Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis:** Current guidelines do not address Rinvoq. Guidelines from the American College of Rheumatology (ACR)/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019) recommend a TNFi as the initial biologic.[8] In those who are secondary non-responders to a TNFi, a second TNFi is recommended over switching out of the class. Both TNFis and interleukin (IL)-17 blockers are recommended over Xeljanz®/XR (tofacitinib tablets/extended release tablets).
- **Atopic Dermatitis:** US-based atopic dermatitis guidelines do not address Rinvoq.[2-4] Phototherapy, followed by systemic therapy, is generally used if initial topical treatments have failed to adequately control the signs and symptoms of disease.[2,4] A variety of systemic agents have been used off-label for treatment of atopic dermatitis, including cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. Biologicals guidelines from the European Academy of Allergy and Clinical Immunology (2021) also do not address Rinvoq.[5,6] Dupixent® (dupilumab subcutaneous injection) is recommended for use in patients ≥ 6 years of age with atopic dermatitis not adequately controlled with topical prescription therapies or when those therapies are not advisable (moderate to severe disease in patients ≥ 12 years of age; severe disease in patients 6 to 11 years of age).

- **Crohn's Disease:** Current guidelines do not address Rinvoq. The American College of Gastroenterology (ACG) has guidelines for Crohn's disease (2018).[11] TNFis are listed as an option for disease that is resistant to corticosteroids, severely active disease, perianal fistulizing disease, and maintenance of remission. In post-operative Crohn's disease, a TNFi should be started within 4 weeks of surgery to prevent recurrence. Guidelines from the American Gastroenterological Association (AGA) [2021] include TNFis among the therapies for moderate to severe Crohn's disease, for induction and maintenance of remission.[12]
- **Psoriatic Arthritis:** Current guidelines do not address Rinvoq. Guidelines from ACR (2018) recommend TNFis over other biologics and Xeljanz for use in treatment-naïve patients with psoriatic arthritis and in those who were previously treated with an oral therapy.[7]
- **Rheumatoid Arthritis:** Guidelines from ACR (2021) recommend addition of a biologic or a targeted synthetic disease-modifying antirheumatic drug (DMARD) for a patient taking the maximum tolerated dose of methotrexate who is not at target.[8]
- **Ulcerative Colitis:** Rinvoq has not yet been addressed in guidelines. Guidelines from the American College of Gastroenterology for ulcerative colitis (2019) note that the following agents can be used for induction of remission in moderately to severely active disease: budesonide extended-release tablets, oral or intravenous systemic corticosteroids, Entyvio® (vedolizumab intravenous infusion), Xeljanz/XR, or TNFis.[9] Guidelines from the American Gastroenterological Association (2020) recommend Xeljanz only after failure of or intolerance to a TNFi.[10]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Rinvoq. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Rinvoq as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Rinvoq to be prescribed by or in consultation with a physician who specializes in the condition being treated.

iii. All reviews for use of Rinvoq for COVID-19 and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rinvoq is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Ankylosing Spondylitis.** Approve for the duration noted if the patient meets ONE of the following criteria (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following criteria (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient meets ONE of the following criteria (a or b):
       - **a)** Patient has had a 3-month trial of at least ONE tumor necrosis factor inhibitor; OR
       - **b)** Patient has tried at least one tumor necrosis factor inhibitor but was unable to tolerate a 3-month trial; AND

Note: Refer to Appendix for examples of tumor necrosis factor inhibitors used for rheumatoid arthritis. Conventional synthetic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine do not count.

iii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Rinvoq. Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following criteria (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Rinvoq); OR
Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondylarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating Rinvoq), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

2. Atopic Dermatitis. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

25. Initial Therapy. Approve for 3 months if the patient meets ALL of the following criteria (i, ii, and iii):

i. Patient is ≥ 12 years of age; AND

ii. Patient meets one of the following criteria (a or b):

a) Patient has had a 3-month trial of at least ONE traditional systemic therapy; OR

b) Patient has tried at least ONE traditional systemic therapy but was unable to tolerate a 3-month trial; AND
Note: Examples of traditional systemic therapies include methotrexate, azathioprine, cyclosporine, and mycophenolate mofetil. A patient who has already tried Dupixent (dupilumab subcutaneous injection) or Adbry (tralokinumab-ldrm subcutaneous injection) is not required to "step back" and try a traditional systemic agent for atopic dermatitis.

iii. The medication is prescribed by or in consultation with an allergist, immunologist, or dermatologist.

26. Patient is Currently Receiving Rinvoq. Approve for 1 year if the patient meets ALL of the following criteria (i, ii, and iii):

i. Patient has been established on therapy for at least at least 90 days; AND
Note: A patient who has received < 90 days of therapy or who is restarting therapy with Rinvoq is reviewed under criterion A (Initial Therapy).

ii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating Rinvoq) in at least one of the following: estimated body surface area affected, erythema, induration/papulation/edema, excoriations, lichenification, and/or a decreased requirement for other topical or systemic therapies for atopic dermatitis; AND

iii. Compared with baseline (prior to receiving Rinvoq), patient experienced an improvement in at least one symptom, such as decreased itching.

3. **Crohn's Disease.** Approve for the duration noted if the patient meets ONE of the following criteria (A or B):
   A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following criteria (i, ii, and iii):
      i. Patient is ≥ 18 years of age; AND
      ii. Patient meets ONE of the following (a or b):
         a) Patient has had a 3-month trial of at least ONE tumor necrosis factor inhibitor; OR
         b) Patient has tried at least one tumor necrosis factor inhibitor but was unable to tolerate a 3-month trial; AND
         Note: Refer to Appendix for examples of tumor necrosis factor inhibitors used for Crohn's disease.
      iii. The medication is prescribed by or in consultation with a gastroenterologist.
   D) Patient is Currently Receiving Rinvoq. Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):
      iv. Patient has been established on therapy for at least 6 months; AND
      C) Note: A patient who has received < 6 months of therapy or who is restarting therapy with Rinvoq is reviewed under criterion A (Initial Therapy).
      ii. Patient meets at least one of the following criteria (a or b):
         a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Rinvoq); OR
         D) Note: Examples of objective measures include fecal markers (e.g., fecal lactoferrin, fecal calprotectin), serum markers (e.g., C-reactive protein), imaging studies (magnetic resonance enterography [MRE], computed tomography enterography [CTE]), endoscopic assessment, and/or reduced dose of corticosteroids.
         c) Compared with baseline (prior to initiating Rinvoq), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or blood in stool.
   E)
4. **Non-Radiographic Axial Spondyloarthritis.** Approve for the duration noted if the patient meets ONE of the following criteria (A or B):
   A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following criteria (i, ii, and iii):
      i. Patient has objective signs of inflammation, defined as at least one of the following (a or b):
         a) C-reactive protein (CRP) elevated beyond the upper limit of normal for the reporting laboratory; OR
         b) Sacroiliitis reported on magnetic resonance imaging (MRI); AND
      ii. Patient meets ONE of the following criteria (a or b):
         a) Patient has had a 3-month trial of at least ONE tumor necrosis factor inhibitor; OR
         b) Patient has tried at least one tumor necrosis factor inhibitor but was unable to tolerate a 3-month trial; AND
         Note: Cimzia (certolizumab pegol subcutaneous injection) is an example of a tumor necrosis factor inhibitor used for non-radiographic axial spondyloarthritis. Conventional synthetic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine do not count.
      iii. The medication is prescribed by or in consultation with a rheumatologist.
   B) Patient is Currently Receiving Rinvoq. Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):
      iii. Patient has been established on the requested drug for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).

iv. Patient meets at least one of the following criteria (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR

Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondylarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

F)

5. Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following criteria (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets ONE of the following criteria (a or b):

a) Patient has had a 3-month trial of at least ONE tumor necrosis factor inhibitor; OR

b) Patient has tried at least one tumor necrosis factor inhibitor but was unable to tolerate a 3-month trial; AND

Note: Refer to Appendix for examples of tumor necrosis factor inhibitors used for psoriatic arthritis. Conventional synthetic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine do not count.

vii. The medication is prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving Rinvoq. Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):

i. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with Rinvoq is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following criteria (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Rinvoq); OR

G) Note: Examples of objective measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsA DAS), Grace Index, Leeds Enthesitis Score (LEI), Spondyloarthritis Consortium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating Rinvoq), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

6. Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following criteria (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets ONE of the following (a or b):

a) Patient has had a 3-month trial of at least ONE tumor necrosis factor inhibitor; OR

b) Patient has tried at least one tumor necrosis factor inhibitor but was unable to tolerate a 3-month trial; AND

Note: Refer to Appendix for examples of tumor necrosis factor inhibitors used for rheumatoid arthritis. Conventional synthetic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine do not count.

iii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Rinvoq. Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):

viii. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with Rinvoq is reviewed under criterion A (Initial Therapy).

ix. Patient meets at least one of the following criteria (a or b):

a) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR

Note: Examples of objective measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).

b) Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

7. Ulcerative Colitis. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following criteria (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets ONE of the following criteria (a or b):

a) Patient has had a 3-month trial of at least ONE tumor necrosis factor inhibitor; OR

b) Patient has tried at least one tumor necrosis factor inhibitor but was unable to tolerate a 3-month trial; AND

Note: Refer to Appendix for examples of tumor necrosis factor inhibitors used for ulcerative colitis.

iii. The medication is prescribed by or in consultation with a gastroenterologist.

H) Patient is Currently Receiving Rinvoq. Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):

i. Patient has been established on therapy for at least 6 months; AND

I) Note: A patient who has received < 6 months of therapy or who is restarting therapy with Rinvoq is reviewed under criterion A (Initial Therapy).

i. Patient meets at least one of the following criteria (a or b):

J) a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Rinvoq); OR

K) Note: Examples of objective measures include fecal markers (e.g., fecal calprotectin), serum markers (e.g., C-reactive protein), endoscopic assessment, and/or reduced dose of corticosteroids.

A) Compared with baseline (prior to initiating Rinvoq), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or rectal bleeding.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rinvoq is not recommended in the following situations:

15. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Rinvoq should not be administered in combination with a biologic used for an inflammatory condition (see Appendix for examples).[1] Combination therapy is generally not recommended due to a potential for a higher rate of adverse effects with combination therapies and lack of evidence supporting additive efficacy. There are no data evaluating combination of Rinvoq with other targeted synthetic DMARDs (e.g., Otezla [apremilast tablets], Xeljanz/XR [tofacitinib tablets/extended-release tablets], Olumiant [baricitinib tablets]); therefore, safety and efficacy of this combination therapy is unknown.

16. **Concurrent Use with a Biologic Immunomodulator.** Rinvoq is not recommended in combination with biologic immunomodulators.[1]
    Note: Examples include Adbry (tralokinumab-ldrm subcutaneous injection), Cinqair (reslizumab intravenous), Dupixent (dupilumab subcutaneous injection), Fasenra (benralizumab subcutaneous injection), Nucala (mepolizumab subcutaneous injection), Tezspire (tezepelumab-ekko subcutaneous injection), and Xolair (omalizumab subcutaneous injection).

17. **Concurrent Use with Other Janus Kinase Inhibitors (JAKis).** Rinvoq is not recommended in combination with other JAKis, such as Cibinqo, Xeljanz/XR, Olumiant.[1]

18. **Concurrent Use with Other Potent Immunosuppressants** (e.g., azathioprine, cyclosporine).[1] Co-administration with other potent immunosuppressive drugs has the risk of added immunosuppression and has not been evaluated in rheumatoid arthritis. Note: This does NOT exclude use of Rinvoq with methotrexate. In rheumatoid arthritis, Rinvoq has been evaluated with background methotrexate and other conventional synthetic disease-modifying antirheumatic drugs (DMARDs).

19. **COVID-19 (Coronavirus Disease 2019).** Forward all requests to the Medical Director.
    Note: This includes requests for cytokine release syndrome associated with COVID-19.

20. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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L) APPENDIX

M) * Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Siliq Prior Authorization Policy
- Siliq® (brodalumab subcutaneous injection – Valeant Pharmaceuticals)

REVIEW DATE: 05/10/2023

OVERVIEW

Siliq, an interleukin (IL)-17A antagonist, is indicated for treatment of adults with moderate to severe **plaque psoriasis** who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.[1] In the pivotal trial, patients were assessed for a response at Week 12.

Guidelines

Joint guidelines from the American Academy of Dermatology and National Psoriasis Medical Board (2019) have been published for management of psoriasis with biologics.[2] These guidelines list Siliq as a monotherapy treatment option for patients with moderate to severe plaque psoriasis. Guidelines from the European Dermatology Forum (2015) recommend biologics (i.e., etanercept, adalimumab, infliximab, Stelara® [ustekinumab subcutaneous injection]) as second-line therapy for induction and long-term treatment if phototherapy and conventional systemic agents have failed, are contraindicated, or are not tolerated.[3]

Safety

Siliq has a Boxed Warning, Risk Evaluation and Mitigation Strategy (REMS) program, and limited distribution program due to risks of suicidal ideation and behavior. The REMS program requires prescribers and pharmacies to be certified to prescribe and/or dispense Siliq.[4] Patients must sign a patient-prescriber agreement form and be aware of the need to seek medical attention for any new/worsening suicidal thoughts or behavior, depression, anxiety, or mood changes.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Siliq. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Siliq as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Siliq to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Siliq is recommended in those who meet the following criteria:

FDA-Approved Indication

YY) Plaque Psoriasis. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following criteria (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets ONE of the following conditions (a or b):

a) Patient has tried at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR

Note: Examples include methotrexate, cyclosporine, acitretin, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already had a 3-month trial or previous intolerance to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for plaque psoriasis. A patient who has already tried a biologic for psoriasis is not required to "step back" and try a traditional systemic agent for psoriasis.

c) Patient has a contraindication to methotrexate, as determined by the prescriber; AND

iii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Siliq. Approve for 1 year if the patient meets ALL of the following criteria (i, ii, and iii):

i. Patient has been established on therapy for at least 90 days; AND
Note: A patient who has received < 90 days of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating Siliq) in at least one of the following: estimated body surface area, erythema, induration/thickness, and/or scale of areas affected by psoriasis; AND

iii. Compared with baseline (prior to receiving Siliq), patient experienced an improvement in at least one symptom, such as decreased pain, itching, and/or burning.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Siliq is not recommended in the following situations:

SSS)

21. **Concurrent Use with other Biologics or with Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs).** Siliq should not be administered in combination with a biologic used for an inflammatory condition (see Appendix for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMRADs has a potential for a higher rate of adverse effects and lacks controlled trial data in support of additive efficacy.
Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Siliq.

22. **Crohn's Disease.** Siliq is contraindicated in patients with Crohn's disease.[1] There is a published Phase II study evaluating Siliq in Crohn's disease (n = 130) that was terminated early due to a disproportionate number of worsening Crohn's disease and lack of efficacy.[5]

23. **Rheumatoid Arthritis.** Efficacy has not been established. A published Phase II study (n = 252) did not demonstrate improvement in American College of Rheumatology 20/50/70 responses with Siliq vs. placebo for treatment of rheumatoid arthritis in patients who had previously failed methotrexate.[6]

24. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

[*] Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARDs – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis.

A) PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Simponi Aria Prior Authorization Policy
- Simponi Aria® (golimumab intravenous infusion – Janssen)

REVIEW DATE: 12/20/2023

OVERVIEW

Simponi Aria, a tumor necrosis factor inhibitor (TNFi), is indicated for the following conditions:[1]

- **Ankylosing spondylitis**, in adults with active disease.
- **Polyarticular juvenile idiopathic arthritis**, in patients ≥ 2 years of age with active disease.
- **Psoriatic arthritis**, in patients ≥ 2 years of age with active disease.
- **Rheumatoid arthritis**, in combination with methotrexate for treatment of adults with moderately to severely active disease.

Simponi Aria is administered by intravenous infusion by a healthcare professional. Efficacy has not been established for patients switching between the Simponi Aria and Simponi subcutaneous.

Guidelines

TNFis feature prominently in guidelines for treatment of inflammatory conditions.

- **Juvenile Idiopathic Arthritis (JIA):** There are guidelines from American College of Rheumatology (ACR) and the Arthritis Foundation for the treatment of JIA (2021) which address oligoarthritis and temporomandibular joint (TMJ) arthritis. For oligoarthritis, a biologic is recommended following a trial of a conventional synthetic DMARD.[9] In patients with TMJ arthritis, scheduled nonsteroidal anti-inflammatory drugs (NSAIDs) and/or intra-articular glucocorticoids are recommended first-line. A biologic is a therapeutic option if there is an inadequate response or intolerance. Additionally, rapid escalation to a biologic ± conventional synthetic DMARD (methotrexate preferred) is often appropriate given the impact and destructive nature of TMJ arthritis. In these guidelines, there is not a preferred biologic that should be initiated for JIA. Simponi (golimumab, route not specified) is among the TNFis recommended in the ACR/Arthritis Foundation guidelines for the treatment of JIA (2019) specific to juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis.[4] TNFis are the biologics recommended for polyarthritis, sacroiliitis, enthesitis. Biologics are recommended following other therapies (e.g., following a conventional synthetic disease-modifying antirheumatic drug [DMARD] for active polyarthritis or following a nonsteroidal anti-inflammatory drug [NSAID] for active JIA with sacroiliitis or enthesitis). However, there are situations where initial therapy with a biologic may be preferred over other conventional therapies (e.g., if there is involvement of high-risk joints such as the cervical spine, wrist, or hip; high disease activity; and/or those judged to be at high risk of disabling joint damage).
- **Psoriatic Arthritis:** Guidelines from ACR (2019) recommend TNFis over other biologics for use in treatment-naïve patients with psoriatic arthritis, and in those who were previously treated with an oral therapy.[5]
- **Rheumatoid Arthritis:** Guidelines from the ACR (2021) recommend addition of a biologic or a targeted synthetic DMARD for a patient taking the maximum tolerated dose of methotrexate who is not at target.[6]
- **Spondyloarthritis:** Guidelines for ankylosing spondylitis and non-radiographic axial spondyloarthritis are published by the ACR/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019).[2] Following primary nonresponse to a TNFi, an

interleukin (IL)-17 blocker is recommended; however, if the patient is a secondary nonresponder, a second TNFi is recommended over switching out of the class. In patients with a contraindication to a TNFi, use of an IL-17 blocker is recommended over traditional oral agents such as methotrexate or sulfasalazine.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Simponi Aria. Because of the specialized skills required for evaluation and diagnosis of patients treated with Simponi Aria as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Simponi Aria to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Simponi Aria is recommended in those who meet one of the following criteria:

FDA-Approved Indications

8. Ankylosing Spondylitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Simponi Aria or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with Simponi Aria or subcutaneous is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Simponi Aria or subcutaneous); OR
Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondyloarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating Simponi Aria or subcutaneous), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

iii.

9. Juvenile Idiopathic Arthritis (JIA). Approve for the duration noted if the patient meets ONE of the following (A or B):

TTT) Note: This includes JIA regardless of type of onset, including a patient with juvenile spondyloarthropathy/active sacroiliac arthritis. JIA is also referred to as Juvenile Rheumatoid Arthritis.

C) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i and ii):

i. Patient meets ONE of the following conditions (a or b):

c) Patient has tried one other medication for this condition; OR

~~**UUU)**~~ Note: Examples of other medications for JIA include methotrexate, sulfasalazine, leflunomide, or a nonsteroidal anti-inflammatory drug (NSAID) [e.g., ibuprofen, naproxen]. A previous trial of a biologic other than the requested medication also counts as a trial of one medication. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for JIA.

d) Patient has aggressive disease, as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a rheumatologist.

D) Patient is Currently Receiving Simponi Aria or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with Simponi Aria or subcutaneous is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Simponi Aria or subcutaneous); OR

Note: Examples of objective measures include Physician Global Assessment (MD global), Parent/Patient Global Assessment of Overall Well-Being (PGA), Parent/Patient Global Assessment of Disease Activity (PDA), Juvenile Arthritis Disease Activity Score (JDAS), Clinical Juvenile Arthritis Disease Activity Score (cJDAS), Juvenile Spondyloarthritis Disease Activity Index (JSpADA), serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

c) Compared with baseline (prior to initiating Simponi Aria or subcutaneous), patient experienced an improvement in at least one symptom, such as improvement in limitation of motion, less joint pain or tenderness, decreased duration of morning stiffness or fatigue, or improved function or activities of daily living.

10. Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist or dermatologist.

B) Patient is Currently Receiving Simponi Aria or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

xxxiii. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with Simponi Aria or subcutaneous is reviewed under criterion A (Initial Therapy).

xxxiv. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Simponi Aria or subcutaneous); OR

iv. Note: Examples of objective measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsA DAS), Grace Index, Leeds Enthesitis Score (LEI), Spondyloarthritis Consortium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating Simponi Aria or subcutaneous), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; or decreased soft tissue swelling in joints or tendon sheaths.

11. Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

B) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):

i. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND

Note: Examples of conventional synthetic DMARDs include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already had a 3-month trial of at least one biologic other than the requested medication. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for rheumatoid arthritis. A patient who has already tried a biologic for rheumatoid arthritis is not required to "step back" and try a conventional synthetic DMARD.

ii. The medication is prescribed by or in consultation with a rheumatologist.

C) Patient is Currently Receiving Simponi Aria or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

xiii. Patient has been established on therapy for at least 6 months; AND

v. Note: A patient who has received < 6 months of therapy or who is restarting therapy with Simponi Aria or subcutaneous is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

b) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR

Note: Examples of objective measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate or C-reactive protein, Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).

vi. b) Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; or decreased soft tissue swelling in joints or tendon sheaths.

vii.

viii.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Simponi Aria is not recommended in the following situations:

6. Concurrent Use with Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD). Data are lacking evaluating concomitant use of Simponi Aria in combination with another biologic or with a targeted synthetic DMARD for an inflammatory condition (see Appendix for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher rate of adverse events with combinations and lack controlled trial data in support of additive efficacy. Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Simponi Aria.

7. Ulcerative Colitis. Simponi subcutaneous injection is indicated for treatment of ulcerative colitis.[7] A single-dose induction study in patients with ulcerative colitis (n = 176) evaluated doses of 1 mg/kg, 2 mg/kg, and 4 mg/kg; however, enrollment was stopped due to lower than expected efficacy in the dose-ranging Phase II portion of the study.[8] Appropriate dosing of Simponi Aria in ulcerative colitis is unclear.

8. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

ix.

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APPENDIX

* Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; PMR – Polymyalgia rheumatic; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Simponi Subcutaneous Prior Authorization Policy
- Simponi® (golimumab subcutaneous injection – Janssen)

REVIEW DATE: 05/10/2023

OVERVIEW

Simponi subcutaneous injection, a tumor necrosis factor inhibitor (TNFi), is approved for the following uses:[1]

- **Ankylosing spondylitis,** in adults with active disease either alone or in combination with methotrexate or other non-biologic disease-modifying antirheumatic drugs (DMARDs).
- **Psoriatic arthritis,** in adults with active disease either alone or in combination with methotrexate or other non-biologic DMARDs.
- **Rheumatoid arthritis,** in adults with moderate to severe active disease in combination with methotrexate.
- **Ulcerative colitis,** for inducing and maintaining clinical response, improving endoscopic appearance of the mucosa during induction, inducing clinical remission, and achieving and sustaining clinical remission in induction responders in adults with moderate to severe disease who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine.

Guidelines

TNFis are featured prominently in guidelines for treatment of inflammatory conditions.

- **Psoriatic Arthritis:** Guidelines from American College of Rheumatology (ACR) [2019] recommend TNFis over other biologics for use in treatment-naïve patients and in those who were previously treated with an oral therapy.[3]
- **Rheumatoid Arthritis:** Guidelines from ACR (2015) have TNFis and non-TNF biologics, administered with or without methotrexate, equally positioned as a recommended therapy following a trial of a conventional synthetic DMARD (e.g., methotrexate, leflunomide, hydroxychloroquine, sulfasalazine).[4]
- **Spondyloarthritis:** Guidelines for ankylosing spondylitis and non-radiographic axial spondylitis are published by the ACR/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019).[2] TNFis are recommended as the initial biologic. In those who are secondary non-responders to a TNFi, a second TNFi is recommended over switching out of the class.
- **Ulcerative Colitis:** Updated American College of Gastroenterology guidelines for ulcerative colitis (2019) note that the following agents can be used for induction of remission in moderately to severely active disease: budesonide tablets; oral or intravenous systemic corticosteroids, Entyvio® (vedolizumab intravenous infusion), Xeljanz®/XR (tofacitinib tablets/extended-release tablets), or TNFis (adalimumab, Simponi subcutaneous, infliximab).[5] In addition to the approved indication, clinical guidelines for the management of pouchitis, published in 2009, indicate that first-line therapy for pouchitis is antibiotic therapy (e.g. metronidazole, ciprofloxacin).[8] Other treatment options include maintenance probiotics, oral or topical budesonide, anti-inflammatory drugs (e.g., mesalamine), or immunosuppressive drugs (e.g., infliximab).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Simponi Subcutaneous. All approvals are provided for the duration listed below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Simponi Subcutaneous as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Simponi Subcutaneous to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Simponi Subcutaneous is recommended in those who meet one of the following criteria:

FDA-Approved Indications

ZZ) Ankylosing Spondylitis. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):
- **A)** Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist.
- **B)** Patient is Currently Receiving Simponi (Subcutaneous or Aria). Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):
  - a. Patient has been established on therapy for at least 6 months; AND
    Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).
  - b. Patient meets at least one of the following criteria (a or b):
    - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Simponi); OR
      Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondylarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).
    - **b)** Compared with baseline (prior to initiating Simponi), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

AAA) Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):
- **A)** Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist or a dermatologist.
- **B)** Patient is Currently Receiving Simponi (Subcutaneous or Aria). Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):
  - **xxxv.** Patient has been established on therapy for at least 6 months; AND
    Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).
  - **xxxvi.** Patient meets at least one of the following (a or b):
    - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Simponi); OR

A) Note: Examples of standardized measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsA DAS), Grace Index, Leeds Enthesitis Score (LEI), Spondyloarthritis Consortium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating Simponi), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

BBB) Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

B) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following criteria (i and ii):

i. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND

Note: Examples of conventional synthetic DMARDs include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already has a 3-month trial with at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for Rheumatoid Arthritis. A patient who has already tried a biologic for rheumatoid arthritis is not required to "step back" and try a conventional synthetic DMARD.

ii. The medication is prescribed by or in consultation with a rheumatologist.

C) Patient is Currently Receiving Simponi (Subcutaneous or Aria). Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):

xiv. Patient has been established on therapy for at least 6 months; AND

D) Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

iii. Patient meets at least one of the following criteria (a or b):

c) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR

Note: Examples of standardized and validated measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).

E) b) Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

CCC) Ulcerative Colitis. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following criteria (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets ONE of the following criteria (a or b):

i. Patient has tried one systemic therapy; OR

Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone or methylprednisolone. A trial of one biologic other than the requested drug also counts as a trial of one systemic agent for ulcerative colitis. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for ulcerative colitis.

ii. Patient meets BOTH of the following criteria [(1) and (2)]:

1. Patient has pouchitis; AND

2. Patient has tried therapy with an antibiotic, probiotic, corticosteroid enema, or Rowasa (mesalamine) enema; AND

Note: Examples of antibiotics include metronidazole and ciprofloxacin. Hydrocortisone enema is an example of a corticosteroid enema.

iii. The medication is prescribed by or in consultation with a gastroenterologist.

E) Patient is Currently Receiving Simponi (Subcutaneous or Aria). Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):

v. Patient has been established on therapy for at least 6 months; AND

F) Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following criteria (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Simponi); OR

G) Note: Examples of assessment for inflammatory response include fecal markers (e.g., fecal calprotectin), serum markers (e.g., C-reactive protein), endoscopic assessment, and/or reduced dose of corticosteroids.

d) Compared with baseline (prior to initiating Simponi), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or decreased rectal bleeding.

H)

Other Uses with Supportive Evidence

xv.

DDD) Spondyloarthritis, Other Subtypes. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

I) Note: This includes undifferentiated arthritis, non-radiographic axial spondyloarthritis, and reactive arthritis (Reiter's disease). For Ankylosing Spondylitis or Psoriatic Arthritis, refer to the respective criteria under FDA-approved indications.

I) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following criteria (i and ii):

i. Patient meets ONE of the following criteria (a or b):

a) Patient meets both of the following criteria [(1) and (2)]:

(1) Patient has arthritis primarily in the knees, ankles, elbows, wrists, hands, and/or feet; AND

(2) Patient has tried at least ONE conventional synthetic disease-modifying antirheumatic drug (DMARD); OR

J) Note: Examples of conventional synthetic DMARDs include methotrexate, leflunomide, and sulfasalazine.

b) Patient has axial spondyloarthritis AND has objective signs of inflammation, defined as at least one of the following criteria [(1) or (2)]:

(1) C-reactive protein elevated beyond the upper limit of normal for the reporting laboratory; OR

(2) Sacroiliitis reported on magnetic resonance imaging; AND

ii. The medication is prescribed by or in consultation with a rheumatologist.

J) Patient is Currently Receiving Simponi (Subcutaneous or Aria). Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):

xxii. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

xxiii. Patient meets at least one of the following criteria (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Simponi); OR

Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS) and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating Simponi), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Simponi Subcutaneous is not recommended in the following situations:

9. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Simponi Subcutaneous should not be administered in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see Appendix for examples). Combination therapy is generally not recommended due to a potentially higher rate of adverse events with combinations and lack of data supportive of additional efficacy.

Note: This does not exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Simponi Subcutaneous.

10. **Plaque Psoriasis without Psoriatic Arthritis.** Simponi Subcutaneous is indicated in patients with psoriatic arthritis, but it has not been evaluated and it is not indicated in patients with plaque psoriasis without psoriatic arthritis. Prospective, controlled trials are needed to determine safety and efficacy in plaque psoriasis. Other TNFis (e.g., etanercept, adalimumab, and infliximab products, Cimzia® [certolizumab pegol subcutaneous injection]) are indicated for the treatment of plaque psoriasis.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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2. Ward MM, Deodhar A, Gensler LS, et al. 2019 update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Rheumatol*. 2019;71(10):1599-1613.
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7. Kavanaugh A, McInnes I, Mease P, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum*. 2009;60:976-986.

APPENDIX

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARDs – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Skyrizi Intravenous Prior Authorization Policy
- Skyrizi® (risankizumab-rzaa intravenous infusion – Abbvie)

REVIEW DATE: 06/28/2023

OVERVIEW

Skyrizi intravenous (IV), an interleukin (IL)-23 blocker, is indicated for **Crohn's disease**, in patients with moderate to severe active disease. In Crohn's disease, a three-dose induction regimen (600 mg at Weeks 0, 4, and 8) is administered by IV infusion. Following induction therapy with the IV product, the recommended maintenance is Skyrizi subcutaneous injection, given as a 360 mg subcutaneous injection administered at Week 12 (4 weeks following the last induction dose), then once every 8 weeks thereafter.

Guidelines

The following guidelines address indications for which Skyrizi IV is indicated.

- **Crohn's Disease:** Skyrizi is not addressed in current guidelines. The American College of Gastroenterology has guidelines for Crohn's disease (2018).[2] Biologics are a treatment option in patients who have moderate to severe disease despite treatment with another agent (e.g., corticosteroid, thiopurine, methotrexate, or tumor necrosis factor inhibitors). Guidelines from the American Gastroenterological Association (2021) include biologics among the therapies for moderate to severe Crohn's disease, for induction and maintenance of remission.[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Skyrizi IV. Because of the specialized skills required for evaluation and diagnosis of patients treated with Skyrizi IV as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Skyrizi IV to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 3 months, which is an adequate duration for the patient to receive three doses.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Skyrizi IV is recommended in those who meet the following:

FDA-Approved Indication

2. Crohn's Disease. Approve three doses for induction if the patient meets the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The medication will be used as induction therapy; AND
- **C)** Patient meets one of the following (i, ii, iii, or iv):
  - **i.** Patient has tried or is currently taking a systemic corticosteroid, or a systemic corticosteroid is contraindicated in this patient; OR
  - **ii.** Patient has tried one other conventional systemic therapy for Crohn's disease; OR

Note: Examples of conventional systemic therapy for Crohn's disease include azathioprine, 6-mercaptopurine, or methotrexate. An exception to the requirement for a trial of or contraindication to steroids or a trial of one other conventional systemic agent can be made if the patient has already tried at least one biologic other than the requested medication. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for Crohn's disease. A trial of mesalamine does not count as a systemic agent for Crohn's disease.

iii. Patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas; OR

iv. Patient had ileocolonic resection (to reduce the chance of Crohn's disease recurrence); AND

D) The medication is prescribed by or in consultation with a gastroenterologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Skyrizi IV is not recommended in the following situations:

25. **Concurrent Use with other Biologics or with Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs).** Data are lacking evaluating concomitant use of Skyrizi with another biologic or with a targeted synthetic DMARD for an inflammatory condition (see Appendix for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher rate of adverse effects and lack controlled trial data in support of additive efficacy.
    Note: This does NOT exclude the use of methotrexate (a traditional systemic agent used to treat Crohn's disease) in combination with Skyrizi.

26. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

95. Skyrizi® [prescribing information]. North Chicago, IL: AbbVie; September 2023.
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97. Feuerstein JD, Ho EY, Shmidt E, et al. AGA clinical practice guidelines on the medical management of moderate to severe luminal and perianal fistulizing Crohn's disease. *Gastroenterology*. 2021;160(7):2496-2508.

APPENDIX

[*] Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Skyrizi Subcutaneous Prior Authorization Policy
- Skyrizi® (risankizumab-rzaa subcutaneous injection – Abbvie)

REVIEW DATE: 06/28/2023

OVERVIEW

Skyrizi subcutaneous (SC), an interleukin (IL)-23 blocker, is indicated for the following uses:[1]

- **Crohn's disease**, in patients with moderate to severe active disease; AND
- **Plaque psoriasis**, for treatment of adults with moderate to severe disease who are candidates for systemic therapy or phototherapy.
- **Psoriatic arthritis**, for treatment of adults with active disease.

Skyrizi is also available in an intravenous formulation that is indicated only in Crohn's disease, given as an IV infusion at Weeks 0, 4, and 8 for induction, followed by Skyrizi SC once every 8 weeks thereafter for maintenance. Skyrizi SC is available as a 180 mg or 360 mg single-dose prefilled cartridge for use with an on-body injector for use in Crohn's disease. For other conditions, Skyrizi is available as a 150 mg single-dose prefilled pen and as a 75 mg or 150 mg prefilled syringe.

Guidelines

The following guidelines address conditions for which Skyrizi SC is indicated.

- **Crohn's Disease:** Skyrizi is not addressed in current guidelines. The American College of Gastroenterology has guidelines for Crohn's disease (2018).[5] Biologics are a treatment option in patients who have moderate to severe disease despite treatment with another agent (e.g., corticosteroid, thiopurine, methotrexate, or tumor necrosis factor inhibitors). Guidelines from the American Gastroenterological Association (2021) include biologics among the therapies for moderate to severe Crohn's disease, for induction and maintenance of remission.[6]
- **Plaque Psoriasis:** Joint guidelines from the American Academy of Dermatology and National Psoriasis Medical Board (2019) have been published for management of psoriasis with biologics.[2] These guidelines list Skyrizi as a monotherapy treatment option for patients with moderate to severe plaque psoriasis. Guidelines from the European Dermatology Forum (2015) recommend biologics (i.e., etanercept, adalimumab, infliximab, Stelara® [ustekinumab SC injection]) as second-line therapy for induction and long-term treatment if phototherapy and conventional systemic agents have failed, are contraindicated, or are not tolerated.[3]
- **Psoriatic Arthritis:** Guidelines from the American College of Rheumatology (2019) recommend tumor necrosis factor inhibitors over other biologics for use in treatment-naïve patients with psoriatic arthritis and in those who were previously treated with an oral therapy.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Skyrizi SC. Because of the specialized skills required for evaluation and diagnosis of patients treated with Skyrizi SC as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Skyrizi SC to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Skyrizi SC is recommended in those who meet one of the following criteria:

FDA-Approved Indications

EEE) Crohn's Disease. Approve Skyrizi Subcutaneous (on-body injector) for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, and iii):

ii. According to the prescriber, the patient will receive induction dosing with Skyrizi intravenous within 3 months of initiating therapy with Skyrizi subcutaneous; AND

iii. Patient meets ONE of the following conditions (a, b, c, or d):

1. Patient has tried or is currently taking corticosteroids, or corticosteroids are contraindicated in this patient; OR
Note: Examples of corticosteroids are prednisone or methylprednisolone.

2. Patient has tried one other conventional systemic therapy for Crohn's disease; OR
Note: Examples of conventional systemic therapy for Crohn's disease include azathioprine, 6-mercaptopurine, or methotrexate. An exception to the requirement for a trial of or contraindication to steroids or a trial of one other conventional systemic agent can be made if the patient has already tried at least one biologic other than the requested medication A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for Crohn's disease. A trial of mesalamine does not count as a systemic agent for Crohn's disease.

3. Patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas; OR

4. Patient had ileocolonic resection (to reduce the chance of Crohn's disease recurrence); AND

iv. The medication is prescribed by or in consultation with a gastroenterologist.

B) Patient is Currently Receiving Skyrizi Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

iii. Patient meets at least one of the following (a or b):

g) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Skyrizi); OR

VVV) Note: Examples of objective measures include fecal markers (e.g., fecal lactoferrin, fecal calprotectin), serum markers (e.g., C-reactive protein), imaging studies (magnetic resonance enterography, computed tomography enterography), endoscopic assessment, and/or reduced dose of corticosteroids.

h) Compared with baseline (prior to initiating Skyrizi), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or blood in stool.

FFF) Plaque Psoriasis. Approve Skyrizi Subcutaneous (pens or syringes) for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets ONE of the following conditions (a or b):

a) Patient has tried at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR

Note: Examples of traditional systemic agents for psoriasis include methotrexate, cyclosporine, acitretin tablets, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already had a 3-month trial or previous intolerance to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for psoriasis. A patient who has already tried a biologic for psoriasis is not required to "step back" and try a traditional systemic agent for psoriasis).

b) Patient has a contraindication to methotrexate, as determined by the prescriber; AND

iii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Skyrizi Subcutaneous. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has been established on the requested drug for at least 90 days; AND
Note: A patient who has received < 90 days of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).

ii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating an the requested drug) in at least one of the following: estimated body surface area, erythema, induration/thickness, and/or scale of areas affected by psoriasis; AND

iii. Compared with baseline (prior to receiving the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain, itching, and/or burning.

GGG) Psoriatic Arthritis. Approve Skyrizi Subcutaneous (pens or syringes) for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving Skyrizi Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

xxxvii. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with Skyrizi is reviewed under criterion A (Initial Therapy).

xxxviii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Skyrizi); OR

WWW) Note: Examples of objective measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsA DAS), Grace Index, Leeds Enthesitis Score (LEI), Spondyloarthritis Consortium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

Compared with baseline (prior to initiating Skyrizi), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; or decreased soft tissue swelling in joints or tendon sheaths.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Skyrizi is not recommended in the following situations:

XXX)

27. **Concurrent Use with other Biologics or with Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs).** Data are lacking evaluating concomitant use of Skyrizi SC with another biologic or with a targeted synthetic DMARD for an inflammatory condition (see Appendix for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher rate of adverse effects and lack controlled trial data in support of additive efficacy.[4]

    Note: This does NOT exclude the use of methotrexate (a traditional systemic agent used to treat psoriasis) in combination with Skyrizi SC.

28. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

YYY)

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102. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol*. 2018;113(4):481-517.
103. Feuerstein JD, Ho EY, Shmidt E, et al. AGA clinical practice guidelines on the medical management of moderate to severe luminal and perianal fistulizing Crohn's disease. *Gastroenterology*. 2021;160(7):2496-2508.

APPENDIX

[*] Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Sotyktu Prior Authorization Policy
- Sotyktu™ (deucravacitinib tablets – Bristol Myers Squibb)

REVIEW DATE: 09/13/2023

OVERVIEW

Sotyktu, a tyrosine kinase 2 (TYK2) inhibitor, is indicated for treatment of moderate to severe **plaque psoriasis** in adults who are candidates for systemic therapy or phototherapy.[1] Limitation of use: Sotyktu is not recommended in combination with potent immunosuppressants.

Guidelines

Guidelines have not been updated to address Sotyktu. Joint guidelines from the American Academy of Dermatology and National Psoriasis Medical Board (2019) have been published for management of psoriasis with biologics.[2] These guidelines list all the biologics approved at the time of publication as agents that may be used as monotherapy for adults with moderate to severe psoriasis. Guidelines from the European Dermatology Forum (2015) recommend biologics (i.e., etanercept, adalimumab, infliximab, Stelara [ustekinumab subcutaneous injection]) as second-line therapy for induction and long-term treatment if phototherapy and conventional systemic agents have failed, are contraindicated, or are not tolerated.[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Sotyktu. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sotyktu as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Sotyktu to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sotyktu is recommended in those who meet the following criteria:

FDA-Approved Indication

2. Plaque Psoriasis. Approve for the duration noted if the patient meets ONE of the following (A or B):
- **A)** Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** Patient meets ONE of the following (a or b):
    - **a)** Patient has tried at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR

      Note: Examples of one traditional systemic agent include methotrexate, cyclosporine, acitretin tablets, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already had a 3-month trial or previous intolerance to at least one biologic other

than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for plaque psoriasis. A patient who has already tried a biologic for psoriasis is not required to "step back" and try a traditional systemic agent for psoriasis.

b) Patient has a contraindication to methotrexate, as determined by the prescriber; AND

iv. The medication is prescribed by or in consultation with a dermatologist.

C) Patient is Currently Receiving Sotyktu. Approve for 1 year meets ALL of the following (i, ii, and iii):

i. Patient has been established on therapy for at least 90 days; AND
Note: A patient who has received < 90 days of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating the requested drug) in at least one of the following: estimated body surface area, erythema, induration/thickness, and/or scale of areas affected by psoriasis; AND

iii. Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain, itching, and/or burning.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sotyktu is not recommended in the following situations:

•

1. **Concurrent Use with other Biologics or with Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs).** Data are lacking evaluating concomitant use of Sotyktu with another biologic or with a targeted synthetic DMARD for an inflammatory condition (see Appendix for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher rate of adverse effects and lack controlled trial data in support of additive efficacy.[4]
   Note: This does NOT exclude the use of methotrexate (a traditional systemic agent used to treat psoriasis) in combination with Sotyktu.

3. **Concurrent use with Other Potent Immunosuppressants, Including Methotrexate**.[1] Co-administration with other potent immunosuppressive drugs has the risk of added immunosuppression and has not been evaluated.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

5. Sotyktu™ tablets [prescribing information]. Princeton, NJ: Bristol Myers Squibb; September 2022.
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7. Nast A, Gisondi P, Ormerod AD, et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris – Update 2015 – Short version – EDF in cooperation with EADV and IPC. *J Eur Acad Dermatol Venereol*. 2015;29(12):2277-2294.

APPENDIX

- * Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Spevigo Prior Authorization Policy
- Spevigo® (spesolimab-sbzo intravenous infusion – Boehringer Ingelheim)

REVIEW DATE: 10/04/2023

OVERVIEW
Spevigo, an interleukin-36 receptor antagonist, is indicated for the treatment of generalized pustular psoriasis flares in adults.[1]

Guidelines
Spevigo is not listed in guidelines for generalized pustular psoriasis.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Spevigo. Because of the specialized skills required for evaluation and diagnosis of patients treated with Spevigo, initial approval requires Spevigo to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 1 month (30 days).

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Spevigo is recommended in those who meet the following criteria:

FDA-Approved Indication

HHH) Generalized Pustular Psoriasis. Approve for up to two doses if the patient meets ALL of the following (A, B, C, and D):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient is experiencing a flare of a moderate-to-severe intensity and meets all of the following (i, ii, iii, and iv)
  - **a)** Patient has Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total score of ≥ 3 points; AND
    Note: The Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total score ranges from 0 (clear skin) to 4 (severe disease).
  - **b)** Patient has a GPPGA pustulation subscore of ≥ 2 points; AND
  - **c)** Patient has new or worsening pustules; AND
  - **d)** Patient has erythema and pustules which affects ≥ 5% of body surface area; AND
- **iii.** If patient has already received Spevigo, patient meets both of the following (i and ii):
  - **1.** Patient has not already received two doses of Spevigo for treatment of the current flare; AND
  - **2.** If this is a new flare, at least 12 weeks have elapsed since the last dose of Spevigo; AND
- **iv.** The medication is prescribed by or in consultation with a dermatologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Spevigo is not recommended in the following situations:

•

29. **Concomitant use with Another Biologic Prescribed for Treatment of Generalized Pustular Psoriasis.** Although not approved, there are case reports documenting use of some biologics approved for plaque psoriasis (see Appendix for examples) for treatment of generalized pustular psoriasis. In the pivotal study, patients were required to discontinue therapy for generalized pustular psoriasis prior to receiving Spevigo.
    Note: Patients with concomitant plaque psoriasis and generalized pustular psoriasis may be receiving a biologic for treatment of plaque psoriasis.

30. **Plaque Psoriasis.** Spevigo has not been studied in patients with plaque psoriasis without generalized pustular psoriasis.
    Note: Patients with concomitant plaque psoriasis and generalized pustular psoriasis may be reviewed under the generalized pustular psoriasis criteria above.

31. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

104. Spevigo® intravenous infusion [prescribing information]. Ridgefield, CT: Boehringer Ingelheim; September 2022.

APPENDIX

[*] Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Stelara Intravenous Prior Authorization Policy
- Stelara® (ustekinumab intravenous infusion – Janssen Biotech)

REVIEW DATE: 06/28/2023

OVERVIEW

Stelara intravenous, a monoclonal antibody against the p40 subunit of the interleukin (IL)-12 and IL-23 cytokines, is indicated in patients ≥ 18 years of age with the following conditions:[1]

- **Crohn's disease**, in patients with moderate to severe active disease; AND
- **Ulcerative colitis**, in patients with moderate to severe active disease.

In Crohn's disease and ulcerative colitis, a single weight-based dose is administered by intravenous infusion. Following induction therapy with the intravenous product, the recommended maintenance is Stelara subcutaneous injection, given as a 90 mg subcutaneous injection administered 8 weeks after the initial intravenous dose, then once every 8 weeks thereafter.

7. Guidelines

8. Guidelines for the treatment of inflammatory conditions recommend use of Stelara.

- **Crohn's Disease:** The American College of Gastroenterology (ACG) has guidelines for Crohn's disease (2018).[2] Stelara is a treatment option in patients who have moderate to severe disease despite treatment with another agent (e.g., corticosteroid, thiopurine, methotrexate, or tumor necrosis factor inhibitors). Guidelines from the American Gastroenterological Association (AGA) [2021] include Stelara among the therapies for moderate to severe Crohn's disease, for induction and maintenance of remission.[5]
- **Ulcerative Colitis:** Stelara is not addressed in the 2019 ACG guidelines for ulcerative colitis.[3] Current guidelines for ulcerative colitis from the AGA (2020) include Stelara among the therapies recommended for moderate to severe disease.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Stelara intravenous. Because of the specialized skills required for evaluation and diagnosis of patients treated with Stelara intravenous as well as the monitoring required for adverse events and long-term efficacy, approval requires Stelara intravenous to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 30 days, which is an adequate duration for the patient to receive one dose.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Stelara intravenous is recommended in those who meet one of the following:

FDA-Approved Indications

3. **Crohn's Disease**. Approve a single dose if the patient meets the following (A, B, C, and D):
   - **E)** Patient is ≥ 18 years of age; AND
   - **F)** The medication will be used as induction therapy; AND
   - **G)** Patient meets one of the following (i, ii, iii, or iv):
     - **i.** Patient has tried or is currently taking a systemic corticosteroid, or a systemic corticosteroid is contraindicated in this patient; OR
     - **ii.** Patient has tried one other conventional systemic therapy for Crohn's disease; OR
       c) Note: Examples of conventional systemic therapy for Crohn's disease include azathioprine, 6-mercaptopurine, or methotrexate. An exception to the requirement for a trial of or contraindication to steroids or a trial of one other conventional systemic agent can be made if the patient has already tried at least one biologic other than the requested medication. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for Crohn's disease. A trial of mesalamine does not count as a systemic agent for Crohn's disease.
     - **iii.** Patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas; OR
     - **iv.** Patient had ileocolonic resection (to reduce the chance of Crohn's disease recurrence); AND
   - **H)** The medication is prescribed by or in consultation with a gastroenterologist.

4. **Ulcerative Colitis.** Approve a single dose if the patient meets the following (A, B, C, and D):
   - **E)** Patient is ≥ 18 years of age; AND
   - **F)** The medication will be used as induction therapy; AND
   - **G)** Patient meets ONE of the following (i or ii):
     - **i.** Patient has tried one systemic therapy; OR
       Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone or methylprednisolone. A trial of one biologic other than the requested medication also counts as a trial of one systemic agent for ulcerative colitis. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for ulcerative colitis.
     - **ii.** Patient meets BOTH of the following (a and b):
       - **d)** Patient has pouchitis; AND
       - **e)** Patient has tried an antibiotic, probiotic, corticosteroid enema, or mesalamine enema; AND
         Note: Examples of antibiotics include metronidazole and ciprofloxacin. Examples of corticosteroid enemas include hydrocortisone enema.
   - **H)** The medication is prescribed by or in consultation with a gastroenterologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Stelara intravenous is not recommended in the following situations:

9. **Ankylosing Spondylitis (AS).** There are other biologic therapies indicated in AS. More data are needed to demonstrate efficacy of Stelara in this condition. There is a published proof-of-concept trial evaluating Stelara in AS (TOPAS – UsTekinumab for the treatment Of Patients with active Ankylosing Spondylitis).[4] TOPAS was a prospective, open-label study evaluating Stelara 90 mg subcutaneous at Week 0, 4, and 16 in patients (n = 20) with AS. After Week 16, patients were followed through Week 28. Patients who previously failed to respond to tumor necrosis factor inhibitor (TNFi) were excluded, but patients who discontinued a TNFi for reasons other than lack of efficacy were allowed to enroll. The primary endpoint was a 40% improvement in disease activity at Week 24 according to the Assessment of SpondyloArthritis International Society (ASAS) criteria (ASAS40). Efficacy analysis

was completed in the intent-to-treat population which included all patients who received at least one dose of Stelara. In all, 65% of patients (95% confidence interval [CI]: 41%, 85%; n = 13/20) achieved an ASAS40 response at Week 24. There was at least a 50% improvement of the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) achieved by 55% of patients (95% CI: 32%, 77%; n = 11/20); improvement in other secondary endpoints were also noted. However, enthesitis (measured by MASES [Maastricht AS Entheses Score] and SPARCC [SPondyloArthritis Research Consortium of Canada] enthesitis indices) and the number of swollen joints were not significantly improved at Week 24. There was a significant reduction of active inflammation on magnetic resonance imaging at Week 24 compared with baseline in sacroiliac joints.

10. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Stelara intravenous should not be administered in combination with another biologic or with a targeted synthetic DMARD for an inflammatory condition (see Appendix for examples). Combination therapy is generally not recommended due to a potential for a higher rate of adverse effects with combinations and lack of additive efficacy. Note: This does NOT exclude the use of conventional agents (e.g., methotrexate, 6-mercaptopurine, azathioprine, and sulfasalazine) in combination with Stelara intravenous.

11. **Plaque Psoriasis.** Stelara for subcutaneous injection is indicated for treatment of plaque psoriasis.[1] Appropriate dosing of Stelara intravenous in plaque psoriasis is unclear.

12. **Psoriatic Arthritis.** Stelara for subcutaneous injection is indicated for treatment of psoriatic arthritis.[1] Appropriate dosing of Stelara intravenous in psoriatic arthritis is unclear.

13. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

9. Stelara [prescribing information]. Horsham, PA: Janssen Biotech; March 2023.
10. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: management of Crohn's Disease in adults. *Am J Gastroenterol*. 2018;113(4):481-517.
11. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114(3):384-413.
12. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterology*. 2020 Apr158(5):1450-1461.
13. Poddubnyy D, Hermann KG, Callhoff J, et al. Ustekinumab for the treatment of patients with active ankylosing spondylitis: results of a 28-week, prospective, open-label, proof-of-concept study (TOPAS). *Ann Rheum Dis*. 2014;73(5):817-823.

APPENDIX

[*] Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Stelara Subcutaneous Prior Authorization Policy with Dosing
- Stelara® (ustekinumab subcutaneous injection – Janssen Biotech)

REVIEW DATE: 06/28/2023

OVERVIEW

Stelara subcutaneous, an interleukin-12/23 blocker, is indicated for the following uses:[1]

- **Crohn's disease**, in patients ≥ 18 years of age with moderate to severe active disease.
- **Plaque psoriasis**, in patients ≥ 6 years of age with moderate to severe disease who are candidates for phototherapy or systemic therapy.
- **Psoriatic arthritis**, in patients ≥ 6 years of age with active disease.
- **Ulcerative colitis**, in patients ≥ 18 years of age with moderate to severe active disease.

Dosing

A weight-based dose is administered by subcutaneous (SC) injection under the supervision of a physician or by the patient or a caregiver. Here is the approved dosing listed in the prescribing information:

- **Crohn's disease:** Starting 8 weeks after an initial intravenous (IV) dose, the maintenance dose is 90 mg SC injection once every 8 weeks (Q8W).
- **Plaque psoriasis:**
  - Adults weighing ≤ 100 kg: 45 mg SC at Week 0, Week 4, and then once every 12 weeks (Q12W) thereafter.
  - Adults weighing > 100 kg: 90 mg SC at Week 0, Week 4, and then Q12W thereafter.
  - Pediatric patients ≥ 6 years of age weighing < 60 kg: 0.75 mg/kg SC at Week 0, Week 4, and then Q12W thereafter.
  - Pediatric patients ≥ 6 years of age weighing 60 kg to 100 kg: 45 mg SC at Week 0, Week 4, and then Q12W thereafter.
  - Pediatric patients ≥ 6 years of age weighing > 100 kg: 90 mg SC at Week 0, Week 4, and then Q12W thereafter.
- **Psoriatic arthritis:**
  - Adults weighing > 100 kg with co-existent moderate to severe plaque psoriasis: 90 mg SC at Week 0, Week 4, and then every Q12W thereafter.
  - All other adults: 45 mg SC at Week 0, Week 4, and then Q12W thereafter.
  - Pediatric patients ≥ 6 years of age weighing < 60 kg: 0.75 mg/kg SC at Week 0, Week 4, and then Q12W thereafter.
  - Pediatric patients ≥ 6 years of age weighing 60 kg to 100 kg: 45 mg SC at Week 0, Week 4, and then Q12W thereafter.
  - Pediatric patients ≥ 6 years of age weighing > 100 kg with co-existent moderate to severe plaque psoriasis: 90 mg SC at Week 0, Week 4, and then Q12W thereafter.
- **Ulcerative colitis:** Starting 8 weeks after an initial IV dose, the maintenance dose is 90 mg SC Q8W.

Guidelines

Guidelines for the treatment of inflammatory conditions recommend use of Stelara subcutaneous.

- **Crohn's Disease:** The American College of Gastroenterology has guidelines for Crohn's disease (2018).[2] Stelara is a treatment option in patients who have moderate to severe disease despite

treatment with another agent (e.g., corticosteroid, thiopurine, methotrexate, or tumor necrosis factor inhibitors [TNFis]).

- **Plaque Psoriasis:** Guidelines (2019) from the American Academy of Dermatology and National Psoriasis Foundation recommend Stelara as a monotherapy treatment option or in combination with other therapies for adults with moderate to severe disease.[3]
- **Psoriatic Arthritis:** Guidelines from the American College of Rheumatology (2018) recommend Stelara after other agents (e.g., TNFis) have been tried.[4] Stelara may be used in patients who have active disease despite treatment with other agents, particularly in those with concomitant inflammatory bowel disease.[4]
- **Ulcerative Colitis:** Guidelines from the American Gastroenterological Association (2020) recommend Stelara for moderate to severe ulcerative colitis.[6] Stelara is not addressed in the 2019 American College of Gastroenterology guidelines for ulcerative colitis.[5] These guidelines note that the following agents can be used for induction of remission in moderately to severely active disease: Uceris® (budesonide extended-release tablets); oral or IV systemic corticosteroids, Entyvio® (vedolizuamb IV infusion), Xeljanz® (tofacitinib tablets, extended-release tablets), or TNFis (adalimumab, Simponi® subcutaneous [golimumab SC injection], infliximab).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Stelara subcutaneous. Because of the specialized skills required for evaluation and diagnosis of patients treated with Stelara subcutaneous as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Stelara subcutaneous to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration listed below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Stelara subcutaneous is recommended in those who meet one of the following criteria:

FDA-Approved Indications

16. Crohn's Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

I) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, and iii):

ii. According to the prescriber, the patient will receive a single induction dose with Stelara intravenous within 2 months of initiating therapy with Stelara subcutaneous; AND

iii. Patient meets one of the following conditions (a, b, c, or d):

b) Patient has tried or is currently taking corticosteroids, or corticosteroids are contraindicated in this patient; OR

c) Patient has tried one conventional systemic therapy for Crohn's disease; OR

Note: Examples of conventional systemic therapy for Crohn's disease include azathioprine, 6-mercaptopurine, or methotrexate. An exception to the requirement for a trial of or contraindication to steroids or a trial of one other conventional systemic agent can be made if the patient has already tried at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for Crohn's disease. A patient who has already received a biologic is not required to "step back" and try another agent.

d) Patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas; OR

e) Patient had ileocolonic resection (to reduce the chance of Crohn's disease recurrence); AND

iv. The medication is prescribed by or in consultation with a gastroenterologist.

J) Patient is Currently Receiving Stelara Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

iii. Patient has been established on the requested drug for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).

iv. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR

17. Note: Examples of objective measures include fecal markers (e.g., fecal lactoferrin, fecal calprotectin), serum markers (e.g., C-reactive protein), imaging studies (magnetic resonance enterography, computed tomography enterography), endoscopic assessment, and/or reduced dose of corticosteroids.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or blood in stool.

18. Plaque Psoriasis. Approve (45 mg syringe/vial) for the duration noted if the patient meets ONE of the following (A or B):

Note: If the 90 mg syringe is requested, approve if the patient meets one of the following:

- patient weighs > 100 kg; OR
- patient is currently receiving the 90 mg syringe; OR
- patient has received standard dosing with the 45 mg syringe/vial for at least 3 months with inadequate efficacy.

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 6 years of age; AND

ii. Patient meets ONE of the following conditions (a or b):

a) Patient has tried at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR
Note: Examples of traditional systemic agents used for psoriasis include methotrexate, cyclosporine, acitretin, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already has a 3-month trial or previous intolerance to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for plaque psoriasis. A patient who has already tried a biologic for psoriasis is not required to "step back" and try a traditional systemic agent for psoriasis.

b) Patient has a contraindication to methotrexate as determined by the prescriber; AND

iii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Stelara Subcutaneous. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has been established on the requested drug for at least 90 days; AND
Note: A patient who has received < 90 days of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).

ii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating an the requested drug) in at least one of the following: estimated body surface area, erythema, induration/thickness, and/or scale of areas affected by psoriasis; AND

iii. Compared with baseline (prior to receiving the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain, itching, and/or burning.

19. Psoriatic Arthritis. Approve (45 mg syringe/vial) for the duration noted if the patient meets ONE of the following (A or B):

Note: If the 90 mg syringe is requested, approve if the patient meets one of the following:

- patient has moderate to severe plaque psoriasis AND weighs > 100 kg; OR
- patient is currently receiving the 90 mg syringe; OR
- patient has received standard dosing with the 45 mg syringe/vial for at least 3 months with inadequate efficacy.

A) Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving Stelara Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

xxxix. Patient has been established on the requested drug for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).

xl. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR

Note: Examples of standardized measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsA DAS), Grace Index, Leeds Enthesitis Score (LEI), Spondyloarthritis Consortium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

20. Ulcerative Colitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

v. According to the prescriber, the patient will receive a single induction dose with Stelara intravenous within 2 months of initiating therapy with Stelara subcutaneous; AND

vi. Patient meets ONE of the following (a or b):

a) Patient has had a trial of one systemic agent for ulcerative colitis; OR

Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone, methylprednisolone. A trial of one biologic other than the requested drug also counts as a trial of one systemic agent for ulcerative colitis. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for ulcerative colitis.

b) Patient meets BOTH of the following [(1) and (2)]:

(1) Patient has pourchitis; AND

(2) Patient has tried an antibiotic, probiotic, corticosteroid enema, or mesalamine enema; AND

Note: Examples of antibiotics include metronidazole and ciprofloxacin. Examples of corticosteroid enemas include hydrocortisone enema.

vii. The medication is prescribed by or in consultation with a gastroenterologist.

B) Patient is Currently Receiving Stelara Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

viii. Patient has been established on the requested drug for at least 6 months; AND

21. Note: A patient who has received < 6 months of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).

ix. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR

22. Note: Examples of assessment for inflammatory response include fecal markers (e.g., fecal calprotectin), serum markers (e.g., C-reactive protein), endoscopic assessment, and/or reduced dose of corticosteroids.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or decreased rectal bleeding.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Stelara subcutaneous is not recommended in the following situations:

K)

14. Ankylosing Spondylitis. There are other biologic therapies indicated in ankylosing spondylitis (e.g., Cimzia® [certolizumab pegol subcutaneous injection], etanercept, adalimumab, infliximab, Simponi subcutaneous, Cosentyx™ [secukinumab subcutaneous injection]). More data are needed to demonstrate efficacy of Stelara in this condition. There is a published proof-of-concept trial evaluating Stelara in ankylosing spondylitis (n = 20).[7] Patients who previously failed to respond to TNFi were excluded, but patients who discontinued a TNFi for reasons other than lack of efficacy were allowed to enroll. In all, 65% of patients (n = 13/20) achieved an ASAS40 response at Week 24. There was at least a 50% improvement of the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) achieved by 55% of patients (n = 11/20). However, enthesitis (measured by MASES [Maastricht AS Entheses Score] and SPARCC [SPondyloArthritis Research Consortium of Canada] enthesitis indices) and the number of swollen joints were not significantly improved at Week 24. There was a significant reduction of active inflammation on magnetic resonance imaging at Week 24 compared with baseline in sacroiliac joints.

15. Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD). Stelara should not be administered in combination with another biologic agent or with a targeted synthetic DMARD used for an inflammatory condition (see Appendix for examples). Combination therapy is generally not recommended due to a potential for a higher rate of adverse effects with combinations and lack of additive efficacy. Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Stelara.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

[*] Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Taltz Prior Authorization Policy
- Taltz® (ixekizumab subcutaneous injection – Eli Lilly)

REVIEW DATE: 05/10/2023

OVERVIEW

A) Taltz, an interleukin (IL)-17A antagonist, is indicated for the following uses:[1]
- **Ankylosing spondylitis**, in adults with active disease.
- **Non-radiographic axial spondyloarthritis**, in adults with active disease and objective signs of inflammation.
- **Plaque psoriasis**, in patients ≥ 6 years of age with moderate to severe disease who are candidates for systemic therapy or phototherapy.
- **Psoriatic arthritis**, in adults with active disease.

B)

C) In the pivotal trial for non-radiographic axial spondyloarthritis, patients were required to have objective signs of inflammation, indicated by elevated C-reactive protein and/or sacroiliitis on magnetic resonance imaging.

Guidelines

- **Spondyloarthritis:** Guidelines for ankylosing spondylitis and non-radiographic axial spondylitis are published by the American College of Rheumatology (ACR)/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019).[2] Following primary non-response to a tumor necrosis factor inhibitor (TNFi), either Cosentyx® (secukinumab subcutaneous injection) or Taltz is recommended; however, if the patient is a secondary non-responder, a second TNFi is recommended over switching out of the class. In patients with a contraindication to a TNFi, use of an IL blocker is recommended over traditional oral agents such as methotrexate or sulfasalazine.
- **Plaque Psoriasis:** Joint guidelines from the American Academy of Dermatology and National Psoriasis Medical Board (2019) have been published for management of psoriasis with biologics.[3] These guidelines list Taltz as a monotherapy treatment option for patients with moderate to severe plaque psoriasis. Guidelines from the European Dermatology Forum (2015) recommend biologics (i.e., etanercept, adalimumab, infliximab, Stelara® (ustekinumab subcutaneous injection) as second-line therapy for induction and long-term treatment if phototherapy and conventional systemic agents have failed, are contraindicated, or are not tolerated.[4]
- **Psoriatic Arthritis:** Guidelines from ACR (2019) recommend TNFis over other biologics for use in treatment-naïve patients with psoriatic arthritis and in those who were previously treated with an oral therapy.[5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Taltz. All approvals are for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Taltz as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Taltz to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Taltz is recommended in those who meet one of the following criteria:

FDA-Approved Indications

III) Ankylosing Spondylitis. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):
- **A)** Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist.
- **B)** Patient is Currently Receiving Taltz. Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):
  - **i.** Patient has been established on therapy for at least 6 months; AND
    Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).
  - **ii.** Patient meets at least one of the following criteria (a or b):
    - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Taltz); OR
      Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondylarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).
    - **b)** Compared with baseline (prior to initiating Taltz), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

2. Non-Radiographic Axial Spondyloarthritis. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):
- **A)** Initial Therapy. Approve for 6 months if the patient meets BOTH of the following criteria (i and ii):
  - **i.** Patient has objective signs of inflammation, defined as at least one of the following (a or b):
    - **a)** C-reactive protein elevated beyond the upper limit of normal for the reporting laboratory; OR
    - **b)** Sacroiliitis reported on magnetic resonance imaging; AND
  - **ii.** The medication is prescribed by or in consultation with a rheumatologist.
- **B)** Patient is Currently Receiving Taltz. Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):
  - **v.** Patient has been established on therapy for at least 6 months; AND
    Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).
  - **vi.** Patient meets at least one of the following criteria (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Taltz); OR

Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing

Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondylarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

3. Plaque Psoriasis. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following criteria (i, ii, and iii):

i. Patient is ≥ 6 years of age; AND

ii. Patient meets ONE of the following criteria (a or b):

1. Patient has tried at least at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR

Note: Examples include methotrexate, cyclosporine, acitretin, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already had a 3-month trial or previous intolerance to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for plaque psoriasis. A patient who has already tried a biologic for psoriasis is not required to "step back" and try a traditional systemic agent for psoriasis.

2. Patient has a contraindication to methotrexate, as determined by the prescriber; AND

iii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Taltz. Approve for 1 year if the patient meets ALL of the following criteria (i, ii, and iii):

i. Patient has been established on therapy for at least 90 days; AND

Note: A patient who has received < 90 days of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating Taltz) in at least one of the following: estimated body surface area, erythema, induration/thickness, and/or scale of areas affected by psoriasis; AND

iii. Compared with baseline (prior to initiating Taltz), patient experienced an improvement in at least one symptom, such as decreased pain, itching, and/or burning.

4. Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

D) Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist or a dermatologist.

E) Patient is Currently Receiving Taltz. Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):

xli. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

xlii. Patient meets at least one of the following criteria (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Taltz); OR

Note: Examples of standardized measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsA DAS), Grace Index, Leeds Enthesitis Score (LEI), Spondyloarthritis Consortium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating Taltz), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Taltz is not recommended in the following situations:

vii.

32. **Concurrent Use with other Biologics or with Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs).** Taltz should not be administered in combination with a biologic used for an inflammatory condition (see Appendix for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher rate of adverse effects and lacks controlled trial data in support of additive efficacy.
    Note: This does NOT exclude the use of methotrexate (a traditional systemic agent used to treat psoriasis) in combination with Taltz.

33. **Inflammatory Bowel Disease (i.e., Crohn's disease, ulcerative colitis).** Exacerbations of inflammatory bowel disease, in some cases serious, occurred in clinical trials with Taltz-treated patients.[1]

34. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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[*] Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARDs – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Tremfya Prior Authorization Policy
- Tremfya® (guselkumab subcutaneous injection – Janssen Biotech/Johnson & Johnson)

REVIEW DATE: 08/23/2023

OVERVIEW

- Tremfya, an interleukin (IL)-23 blocker, is indicated for the following uses:[1]
  - **Plaque psoriasis**, in adults with moderate to severe disease who are candidates for systemic therapy or phototherapy.
  - **Psoriatic arthritis**, in adults with active disease (given ± a conventional synthetic disease-modifying antirheumatic drug).
-

Guidelines

IL blockers are mentioned in guidelines for treatment of inflammatory conditions.

- **Plaque Psoriasis:** Joint guidelines from the American Academy of Dermatology and National Psoriasis Medical Board (2019) have been published for management of psoriasis with biologics.[2] These guidelines list Tremfya as a monotherapy treatment option for patients with moderate to severe plaque psoriasis. It is recommended that a response to therapy be ascertained after 12 weeks of continuous therapy. Guidelines from the European Dermatology Forum (2015) recommend biologics (i.e., etanercept, adalimumab, infliximab, Stelara® [ustekinumab subcutaneous injection]) as second-line therapy for induction and long-term treatment if phototherapy and conventional systemic agents have failed, are contraindicated, or are not tolerated.[3]
- **Psoriatic Arthritis:** Guidelines from the American College of Rheumatology/National Psoriasis Foundation (2018) were published prior to approval of Tremfya for psoriatic arthritis. However, these guidelines generally recommend tumor necrosis factor inhibitors as the first-line treatment strategy over other biologics (e.g., IL-17 blockers, IL-12/23 inhibitor) with differing mechanisms of action.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tremfya. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tremfya as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Tremfya to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tremfya is recommended in those who meet one of the following criteria:

FDA-Approved Indications

JJJ) Plaque Psoriasis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets ONE of the following conditions (a or b):

a) Patient has tried at least at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR

Note: Examples include methotrexate, cyclosporine, acitretin, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already had a 3-month trial or previous intolerance to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for psoriasis. A patient who has already tried a biologic for psoriasis is not required to "step back" and try a traditional systemic agent for psoriasis.

b) Patient has a contraindication to methotrexate, as determined by the prescriber; AND

iii. The requested agent is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Tremfya. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has been established on the requested drug for at least 90 days; AND

Note: A patient who has received < 90 days of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).

ii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating the requested drug) in at least one of the following: estimated body surface area, erythema, induration/thickness, and/or scale of areas affected by psoriasis; AND

iii. Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain, itching, and/or burning.

KKK) Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if Tremfya is prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving Tremfya. Approve for 1 year if the patient meets BOTH of the following (i and ii):

xliii. Patient has been established on the requested drug for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).

xliv. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR

Note: Examples of objective measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsADAS), Grace Index, Leeds Enthesitis Score (LEI), Spondyloarthritis Consortium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue;

improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tremfya is not recommended in the following situations:

110.

35. Concurrent Use with other Biologics or with Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs). Data are lacking evaluating concomitant use of Tremfya in combination with another biologic or with a targeted synthetic DMARD for an inflammatory condition (see Appendix for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher rate of adverse effects and lack controlled trial data in support of additive efficacy.

Note: This does NOT exclude the use of methotrexate (a traditional systemic agent used to treat psoriasis) in combination with Tremfya.

36. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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- * Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Velsipity Prior Authorization Policy
- Velsipity® (etrasimod tablets – Pfizer)

REVIEW DATE: 11/08/2023

OVERVIEW

Velsipity, a sphingosine 1-phosphate receptor modulator, is indicated for the treatment of **ulcerative colitis** (UC), in adults with moderately to severely active disease.[1]

Guidelines/Clinical Efficacy

Velsipity is not currently addressed in UC guidelines. The American Gastroenterological Association (2020) and the American College of Gastroenterology (2019) have clinical practice guidelines on the management of moderate to severe UC and make recommendations for induction and maintenance of remission in adults.[2,3] Both endorse the use of biologic agents and give specific patient circumstances in the selection for induction and maintenance therapies. Pivotal trials for Velsipity included adults with moderately to severely active UC who had an inadequate response or were intolerant to any of the following agents: oral aminosalicylates, corticosteroids, immunomodulators (e.g., 6-mercaptopurine and azathioprine), or a biologic (e.g., tumor necrosis factor inhibitor, Entyvio® [vedolizumab injection], or a Janus kinase inhibitor (e.g., Xeljanz® [tofacitinib tablets]).[1]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Velsipity. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Velsipity as well as the monitoring required for adverse events and long-term efficacy, approval requires Velsipity to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Velsipity is recommended in those who meet one of the following criteria:

FDA-Approved Indications

3. Ulcerative Colitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

C) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient has had a trial of ONE systemic agent for ulcerative colitis; AND
Note: Examples of systemic agents for ulcerative colitis include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone, methylprednisolone. A trial of one biologic also counts as a trial of one systemic agent for ulcerative colitis. Refer to the Appendix for examples of biologics used for ulcerative colitis.

iii. The medication is prescribed by or in consultation with a gastroenterologist.

F) Patient is Currently Receiving Velsipity. Approve for 1 year if the patient meets BOTH of the following (i and ii):

vi. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR

Note: Examples of assessment for inflammatory response include fecal markers (e.g., fecal calprotectin), serum markers (e.g., C-reactive protein), endoscopic assessment, and/or reduced dose of corticosteroids.

c) Compared with baseline (prior to initiating Velsipity), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or decreased rectal bleeding.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Velsipity is not recommended in the following situations:

37. Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD) for Ulcerative Colitis. In the pivotal trials, patients who received Velsipity were not permitted to receive concomitant treatment with biologics used for the treatment of ulcerative colitis (see Appendix for examples).[1] Combination therapy is generally not recommended due to a potential for a higher rate of adverse effects with combinations and lack of evidence supporting additive efficacy. There are no data evaluating combination of Velsipity with a targeted synthetic DMARD (e.g., Xeljanz/Xeljanz XR (tofacitinib tablets/extended-release tablets); therefore, safety and efficacy of this combination is unknown.

38. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

[*] Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Xeljanz/Xeljanz XR Prior Authorization Policy
- Xeljanz®/Xeljanz XR (tofacitinib tablets, oral solution/extended-release tablets – Pfizer)

REVIEW DATE: 09/06/2023

OVERVIEW

Xeljanz/Xeljanz XR is an inhibitor of the Janus kinases pathways.[1] Xeljanz/Xeljanz XR tablets are approved for the following uses:

- **Ankylosing spondylitis**, in adults with active disease who have had an inadequate response or intolerance to one or more tumor necrosis factor inhibitors (TNFis).
- **Polyarticular juvenile idiopathic arthritis (JIA)**, in patients ≥ 2 years of age with active disease who have had an inadequate response or intolerance to one or more TNFis. Note: This indication is for Xeljanz only (not the XR formulation).
- **Psoriatic arthritis**, in adults with active disease who have had an inadequate response or intolerance to one or more TNFis. In psoriatic arthritis, Xeljanz/Xeljanz XR should be used in combination with a conventional synthetic disease-modifying antirheumatic drug (DMARD).
- **Rheumatoid arthritis**, in adults with moderately to severely active disease who have had an inadequate response or intolerance to one or more TNFis.
- **Ulcerative colitis**, in adults with moderately to severely active disease who have had an inadequate response or who are intolerant to one or more TNFis.

Xeljanz oral solution is only indicated for **polyarticular JIA**.

For all indications, Xeljanz/Xeljanz XR is not recommended for use in combination with biologics or potent immunosuppressants such as azathioprine or cyclosporine.

Guidelines

Guidelines for the treatment of inflammatory conditions recommend use of Xeljanz/Xeljanz XR.

- **Ankylosing Spondylitis:** Guidelines from the American College of Rheumatology (ACR)/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019) recommend TNFis as the initial biologic.[8] In those who are secondary non-responders to a TNFi, a second TNFi is recommended over switching out of the class. Both TNFis and interleukin-17 blockers are recommended over Xeljanz/Xeljanz XR.
- **JIA:** Xeljanz is not addressed in ACR/Arthritis Foundation guidelines for the treatment of JIA (2019) specific to juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis.[2] TNFis are the biologics recommended for polyarthritis, sacroiliitis, and enthesitis. Actemra® (tocilizumab intravenous infusion, tocilizumab subcutaneous injection) and Orencia® (abatacept intravenous infusion, abatacept subcutaneous injection) are also among the biologics recommended for polyarthritis. Biologics are recommended following other therapies (e.g., following DMARDs for active polyarthritis or following a nonsteroidal anti-inflammatory drug for active JIA with sacroiliitis or enthesitis). However, there are situations where initial therapy with a biologic may be preferred over other conventional therapies (e.g., if there is involvement of high-risk joints such as the cervical spine, wrist, or hip; high disease activity; and/or those judged to be at high risk of disabling joint damage).

- **Psoriatic arthritis:** Guidelines from ACR (2018) recommend TNFis over other biologics and Xeljanz for use in treatment-naïve patients with psoriatic arthritis and in those who were previously treated with an oral therapy.[3]
- **Rheumatoid arthritis:** Guidelines from ACR (2021) recommend addition of a biologic or a targeted synthetic DMARD for a patient taking the maximum tolerated dose of methotrexate who is not at target.[4]
- **Ulcerative colitis:** Guidelines from the American College of Gastroenterology for ulcerative colitis (2019) note that the following agents can be used for induction of remission in moderately to severely active disease: budesonide extended-release tablets; oral or intravenous systemic corticosteroids, Entyvio® (vedolizumab intravenous infusion), Xeljanz, or TNFis.[5] Guidelines from the American Gastroenterological Association (2020) recommend Xeljanz only after failure of or intolerance to a TNFi.[6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Xeljanz/Xeljanz XR. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of a patient treated with Xeljanz/Xeljanz XR as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Xeljanz/Xeljanz XR to be prescribed by or in consultation with a physician who specializes in the condition being treated.

B) All reviews for use of Xeljanz/Xeljanz XR for COVID-19 and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xeljanz/Xeljanz XR is recommended in those who meet one of the following criteria:

FDA-Approved Indications

12. Ankylosing Spondylitis. Approve Xeljanz/Xeljanz XR tablets (not oral solution) for the duration noted if the patient meets ONE of the following (A or B):

C) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets ONE of the following (a or b):

c) Patient has had a 3-month trial of at least ONE tumor necrosis factor inhibitor; OR

d) Patient has tried at least one tumor necrosis factor inhibitor but was unable to tolerate a 3-month trial; AND

Note: Refer to Appendix for examples of tumor necrosis factor inhibitors used for rheumatoid arthritis. Conventional synthetic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine do not count.

iv. The medication is prescribed by or in consultation with a rheumatologist.

D) Patient is Currently Receiving Xeljanz/Xeljanz XR. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Xeljanz/Xeljanz XR); OR

Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondylarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating Xeljanz/Xeljanz XR), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

C)

13. **Juvenile Idiopathic Arthritis (JIA).** Approve Xeljanz tablets (not the Xeljanz XR formulation) or oral solution for the duration noted if the patient meets ONE of the following (A or B):

D) Note: This includes JIA regardless of type of onset and a patient with juvenile spondyloarthropathy/active sacroiliac arthritis. JIA is also referred to as Juvenile Rheumatoid Arthritis.

E) Initial Therapy. Approve for 6 months if the patient meets the following (i and ii):

i. Patient meets ONE of the following (a or b):

e) Patient has had a 3-month trial of at least one tumor necrosis factor inhibitor; OR

f) Patient has tried at least one tumor necrosis factor inhibitor but was unable to tolerate a 3-month trial; AND

~~**E)**~~ Note: Refer to Appendix for examples of tumor necrosis factor inhibitors. Conventional synthetic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine do not count.

i. The medication is prescribed by or in consultation with a rheumatologist.

F) Patient is Currently Receiving Xeljanz. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with Xeljanz is reviewed under criterion A (Initial Therapy).

viii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Xeljanz); OR

Note: Examples of objective measures include Physician Global Assessment (MD global), Parent/Patient Global Assessment of Overall Well-Being (PGA), Parent/Patient Global Assessment of Disease Activity (PDA), Juvenile Arthritis Disease Activity Score (JDAS), Clinical Juvenile Arthritis Disease Activity Score (cJDAS), Juvenile Spondyloarthritis Disease Activity Index (JSpADA), serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating Xeljanz), patient experienced an improvement in at least one symptom, such as improvement in limitation of motion, less joint pain or tenderness, decreased duration of morning stiffness or fatigue, improved function or activities of daily living.

G)

14. **Psoriatic Arthritis.** Approve Xeljanz/Xeljanz XR tablets (not oral solution) for the duration noted if the patient meets ONE of the following (A or B):

C) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, and iv):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient meets ONE of the following (a or b):
  - **a)** Patient has had a 3-month trial of at least ONE tumor necrosis factor inhibitor ; OR
  - **b)** Patient has tried at least one tumor necrosis factor inhibitor but was unable to tolerate a 3-month trial; AND

    Note: Refer to Appendix for examples of tumor necrosis factor inhibitors used for psoriatic arthritis. Conventional synthetic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine do not count.
- **ix.** The medication will be used in combination with methotrexate or another conventional synthetic disease-modifying antirheumatic drug (DMARD), unless contraindicated; AND

  Note: Examples of other conventional synthetic DMARDs include leflunomide and sulfasalazine.
- **x.** The medication is prescribed by or in consultation with a rheumatologist or a dermatologist.

D) Patient is Currently Receiving Xeljanz/Xeljanz XR. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient has been established on therapy for at least 6 months; AND

  Note: A patient who has received < 6 months of therapy or who is restarting therapy with Xeljanz/Xeljanz XR is reviewed under criterion A (Initial Therapy).
- **ii.** The medication will be used in combination with methotrexate or another conventional synthetic disease-modifying antirheumatic drug (DMARD), unless contraindicated; AND

  Note: Examples of other conventional synthetic DMARDs include leflunomide and sulfasalazine.
- **iii.** Patient meets at least one of the following (a or b):
  - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Xeljanz/Xeljanz XR); OR

    F) Note: Examples of standardized measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsA DAS), Grace Index, Leeds Enthesitis Score (LEI), Spondyloarthritis Consortium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).
  - **c)** Compared with baseline (prior to initiating Xeljanz/Xeljanz XR), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

15. Rheumatoid Arthritis. Approve Xeljanz/Xeljanz XR tablets (not oral solution) for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient meets ONE of the following (a or b):
  - **a)** Patient has had a 3-month trial of at least ONE tumor necrosis factor inhibitor; OR
  - **b)** Patient has tried at least one tumor necrosis factor inhibitor but was unable to tolerate a 3-month trial; AND

    Note: Refer to Appendix for examples of tumor necrosis factor inhibitors used for rheumatoid arthritis. Conventional synthetic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine do not count.

iii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Xeljanz/Xeljanz XR. Approve for 1 year if the patient meets BOTH of the following (i and ii):

xvi. Patient has been established on therapy for at least 6 months; AND

G) Note: A patient who has received < 6 months of therapy or who is restarting therapy with Xeljanz/Xeljanz XR is reviewed under criterion A (Initial Therapy).

iv. Patient meets at least one of the following (a or b):

d) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR

Note: Examples of objective measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).

b) Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

16. Ulcerative Colitis. Approve Xeljanz/Xeljanz XR tablets (not oral solution) for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets ONE of the following (a or b):

a) Patient has had a 3-month trial of at least ONE tumor necrosis factor inhibitor; OR

b) Patient has tried at least one tumor necrosis factor inhibitor but was unable to tolerate a 3-month trial; AND

Note: Refer to Appendix for examples of tumor necrosis factor inhibitors used for ulcerative colitis.

iii. The medication is prescribed by or in consultation with a gastroenterologist.

G) Patient is Currently Receiving Xeljanz/Xeljanz XR. Approve for 1 year if the patient meets BOTH of the following (i and ii):

vii. Patient has been established on therapy for at least 6 months; AND

H) Note: A patient who has received < 6 months of therapy or who is restarting therapy with Xeljanz/Xeljanz XR is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Xeljanz/Xeljanz XR); OR

I) Note: Examples of objective measures include fecal markers (e.g., fecal calprotectin), serum markers (e.g., C-reactive protein), endoscopic assessment, and/or reduced dose of corticosteroids.

d) Compared with baseline (prior to initiating Xeljanz/Xeljanz XR), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or decreased rectal bleeding.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xeljanz/Xeljanz XR is not recommended in the following situations:

39. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Xeljanz/Xeljanz XR should not be administered in combination with a biologic used for an inflammatory condition (see Appendix for examples).[1] Combination therapy is generally not recommended due to a potential for a higher rate of adverse effects with combinations and lack of evidence supporting additive efficacy. There are no data evaluating combination of Xeljanz/Xeljanz XR with a targeted synthetic DMARD; therefore, safety and efficacy of these combinations are unknown.

40. **Concurrent use with Other Potent Immunosuppressants** (e.g., azathioprine, tacrolimus, cyclosporine, mycophenolate mofetil).[1] Co-administration with other potent immunosuppressive drugs has the risk of added immunosuppression and has not been evaluated in rheumatoid arthritis. In ulcerative colitis, Xeljanz is not recommended for use in combination with potent immunosuppressants such as azathioprine and cyclosporine.
    Note: This does NOT exclude use of Xeljanz/Xeljanz XR with methotrexate for rheumatoid arthritis; Xeljanz/Xeljanz XR has been evaluated in patients with rheumatoid arthritis taking background methotrexate, leflunomide, or combinations of disease-modifying antirheumatic drugs (DMARDs) containing methotrexate and/or leflunomide.

41. **COVID-19 (Coronavirus Disease 2019).** Forward all requests to the Medical Director.
    Note: This includes requests for cytokine release syndrome associated with COVID-19.

42. **Renal Transplantation.** More data are needed. A Phase IIb study in kidney transplant patients (n = 331) found Xeljanz was equivalent to cyclosporine in preventing acute rejection.[7] However, based on Phase IIb studies, there are concerns of Epstein Barr Virus-associated post-transplant lymphoproliferative disorder in certain transplant patients receiving Xeljanz.[1,6]

43. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

* Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Zymfentra Prior Authorization Policy
- Zymfentra® (infliximab-dyyb subcutaneous injection – Celltrion)

REVIEW DATE: 12/06/2023

OVERVIEW

3. Zymfentra, a subcutaneous (SC) tumor necrosis factor (TNF) inhibitor, is indicated for the following uses:[1]

- **Crohn's disease**, as maintenance treatment for moderately to severely active disease in adults who have received three induction doses with an infliximab intravenous product.
- **Ulcerative colitis**, as maintenance treatment for moderately to severely active disease in adults who have received three induction doses with an infliximab intravenous product.

4.

5. Therapy begins with an infliximab intravenous (IV) product administered as an induction regimen at Weeks 0, 2, and 6.[1] At Week 10 or at any scheduled infliximab IV infusion in patients with a clinical response or remission, therapy can be switched to Zymfentra. The recommended dose of Zymfentra is 120 mg administered subcutaneously once every 2 weeks. In the pivotal studies evaluating Zymfentra, all patients had previously tried corticosteroids and/or conventional agents for Crohn's disease and ulcerative colitis.

Guidelines

Guidelines for the treatment of inflammatory conditions recommend use of infliximab.

- **Crohn's Disease:** The American College of Gastroenterology (ACG) has guidelines for Crohn's disease (2018).[2] TNFis are listed as an option for disease that is resistant to corticosteroids, severely active disease, perianal fistulizing disease, and maintenance of remission. In post-operative Crohn's disease, a TNFi should be started within 4 weeks of surgery to prevent recurrence. Guidelines from the American Gastroenterological Association (AGA) [2021] include infliximab among the therapies for moderate to severe Crohn's disease, for induction and maintenance of remission.[3]
- **Ulcerative Colitis:** ACG guidelines for ulcerative colitis (2019) note that the following agents can be used for induction of remission in moderately to severely active disease: budesonide extended-release tablets; oral or intravenous systemic corticosteroids, Entyvio® (vedolizumab intravenous infusion), Xeljanz®/XR (tofacitanib tablets/extended-release tablets), or TNFis.[4] Guidelines from the AGA (2020) include infliximab amongst the therapies recommended for moderate to severe ulcerative colitis.[5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zymfentra. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zymfentra as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Zymfentra to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Zymfentra is recommended in those who meet one of the following:

FDA-Approved Indications

10. Crohn's Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

C) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, and iv):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** According to the prescriber, the patient is currently receiving infliximab intravenous maintenance therapy or will receive induction dosing with an infliximab intravenous product within 3 months of initiating therapy with Zymfentra; AND
- **iii.** Patient meets ONE of the following (a, b, c, or d):
  - **a)** Patient has tried or is currently taking systemic corticosteroids, or corticosteroids are contraindicated in this patient; OR
    Note: Examples of corticosteroids are prednisone and methylprednisolone.
  - **b)** Patient has tried one conventional systemic therapy for Crohn's disease; OR
    Note: Examples of conventional systemic therapy for Crohn's disease include azathioprine, 6-mercaptopurine, or methotrexate. An exception to the requirement for a trial of or contraindication to steroids or a trial of one other conventional systemic agent can be made if the patient has already tried at least one biologic other than the requested medication. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for Crohn's disease. A trial of mesalamine does not count as a systemic therapy for Crohn's disease.
  - **c)** Patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas; OR
  - **d)** Patient had ileocolonic resection (to reduce the chance of Crohn's disease recurrence); AND
- **iv.** The medication is prescribed by or in consultation with a gastroenterologist; OR

D) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **i.** Patient has been established on therapy for at least 6 months; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).
- **ii.** Patient meets at least one of the following (a or b):

i) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested product); OR

ii. Note: Examples of objective measures include fecal markers (e.g., fecal lactoferrin, fecal calprotectin), serum markers (e.g., C-reactive protein), imaging studies (magnetic resonance enterography [MRE], computed tomography enterography [CTE]), endoscopic assessment, and/or reduced dose of corticosteroids.

a) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or blood in stool.

6. **Ulcerative Colitis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   C) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, and iv):
      i. Patient is ≥ 18 years of age; AND
      ii. According to the prescriber, the patient is currently receiving infliximab intravenous maintenance therapy or will receive induction dosing with an infliximab intravenous product within 3 months of initiating therapy with Zymfentra; AND
      iii. Patient meets ONE of the following (a or b):
         c) Patient had a trial of one systemic agent or was intolerant to one of these agents for ulcerative colitis; OR
         Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone or methylprednisolone. A trial of a mesalamine product does not count as a systemic therapy for ulcerative colitis. A previous trial of one biologic other than the requested medication also counts as a trial of one systemic agent for ulcerative colitis. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for ulcerative colitis.
         d) Patient meets BOTH of the following [(1) and (2)]:
            (3) Patient has pouchitis; AND
            (4) Patient has tried therapy with an antibiotic, probiotic, corticosteroid enema, or Rowasa® (mesalamine enema); AND
            Note: Examples of antibiotics include metronidazole and ciprofloxacin. Examples of corticosteroid enemas include hydrocortisone enema (Cortenema, generics).
      iv. The medication is prescribed by or in consultation with a gastroenterologist.
   H) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):
      viii. Patient has been established on therapy for at least 6 months; AND
      iii. Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).
      ii. Patient meets at least one of the following (a or b):
         a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR
         iv. Note: Examples of objective measures include fecal markers (e.g., fecal calprotectin), serum markers (e.g., C-reactive protein), endoscopic assessment, and/or reduced dose of corticosteroids.
   e) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or rectal bleeding.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zymfentra is not recommended in the following situations:

16. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Data are lacking evaluating concomitant use of an infliximab product in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see APPENDIX for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher rate of AEs and lack controlled trial data in support of additive efficacy.
    Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with an infliximab product.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

[*] Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

PRIOR AUTHORIZATION POLICY

POLICY: Inpefa Prior Authorization Policy
- Inpefa™ (sotagliflozin tablets – Lexicon)

REVIEW DATE: 06/14/2023

OVERVIEW

Inpefa, a sodium glucose co-transporter-2 (SGLT-2) inhibitor, is indicated **to reduce the risk of cardiovascular (CV) death, hospitalization for heart failure (HHF), and urgent heart failure visit in adults** with[1]:

- Heart failure; OR
- Type 2 diabetes mellitus, chronic kidney disease (CKD), and other CV risk factors.

Unlike other SGLT-2 inhibitors, Inpefa is not indicated for glycemic control.

Guidelines

The pivotal data with Inpefa are mentioned in many available guidelines. However, formal recommendations for Inpefa are not provided; the agent was not approved at the time guidelines were written. SGLT-2 inhibitors are recommended as first-line treatment for heart failure in the American Heart Association/American College of Cardiology (ACC)/Heart Failure Society of America joint guideline for the management of heart failure (2022).[2] The pivotal trial with Inpefa in patients with heart failure is noted to extend the benefits of SGLT-2 inhibitors to patients with diabetes and acutely decompensated heart failure.[5] A 2023 ACC expert consensus statement notes the benefit of SGLT-2 inhibitors as part of guideline-directed medical therapy in patients with heart failure with preserved ejection fraction (HFpEF).[8] According to the ACC expert consensus statement, SGLT-2 inhibitors (Jardiance, Farxiga) should be initiated in all individuals with HFpEF who are stable during hospitalization and have no contraindications. The pivotal heart failure trial with Inpefa is mentioned, and it is noted that Inpefa treatment resulted in a significantly lower total number of deaths from CV causes, HHF, and urgent visits for heart failure than placebo, regardless of left ventricular ejection fraction.

The Kidney Diseases: Improving Global Outcomes (KDIGO) clinical practice guideline for diabetes management in CKD (2022) and the American Diabetes Association (ADA)/KDIGO diabetes management in CKD consensus report (2022) recommend an SGLT-2 with proven kidney or CV benefit for patients with type 2 diabetes, CKD, and estimated glomerular filtration rate (eGFR) ≥ 20 mL/min/1.73 m^2.[4,6] SGLT-2 inhibitors are recommended independent of hemoglobin A_{1c} (HbA_{1c}) or the need for additional glucose lowering. This recommendation is based on strong evidence that SGLT-2 inhibitors reduce CKD progression, heart failure, and atherosclerotic CV disease (ASCVD) risk in patients with type 2 diabetes and CKD. Results from pivotal trials with Inpefa are briefly mentioned.

The ADA standards of care (2023) recommend an SGLT-2 inhibitor or glucagon-like peptide-1 (GLP-1) agonist with demonstrated CV disease benefit as part of the glucose lowering regimen and comprehensive CV risk reduction strategy, independent of HbA_{1c} in patients with established CV disease or indicators of high CV risk, established kidney disease, or heart failure.[3] An ADA and European Association for the Study of Diabetes consensus statement on the management of type 2 diabetes (2022) is reflected in the ADA standards of care.[9]

The American Association of Clinical Endocrinology (AACE) comprehensive type 2 diabetes management algorithm (2023) builds on the 2022 AACE clinical practice guideline on diabetes.[5,7] SGLT-2 inhibitors with 'proven benefit' are an alternative to GLP-1 agonists to reduce the risk of major adverse CV or CV death in patients with type 2 diabetes and established CV disease. For patients with type 2 diabetes and established ASCVD or at high risk for ASCVD, the use of an SGLT-2 inhibitor reduces the risk of HHF and in patients with heart failure and/or CKD, SGLT-2 inhibitors should be used as first-line therapy. SGLT-2 inhibitors are recommended in patients with type 2 diabetes and heart failure regardless of glycemic goal or other antihyperglycemic treatments. There are robust data for the benefit of SGLT-2 inhibitors to reduce adverse renal outcomes. Use of an SGLT-2 inhibitor with 'proven benefits' is recommended as initial therapy to reduce the progression of diabetic kidney disease and CV disease risk for patients with type 2 diabetes and diabetic kidney disease with eGFR ≥ 25 mL/min/1.73 m^2 or ≥ 20 mL/min/1.73 m^2 if heart failure is also present.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Inpefa. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Inpefa is recommended in those who meet the following criteria:

FDA-Approved Indication(s)

138. Heart Failure, to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit. Approve for 1 year if the patient is ≥ 18 years of age.

139. Type 2 Diabetes, to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit. Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) Patient is ≥ 18 years of age; AND
B) Patient has chronic kidney disease; AND
C) Patient has one or more cardiovascular risk factor(s), according to the prescriber.
Note: Patients with heart failure should be reviewed under criteria for *Heart Failure.*

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Inpefa is not recommended in the following situations:

195. Type 1 Diabetes. Inpefa is not approved for glycemic control. Note: Patients with heart failure should be reviewed under criteria for *Heart Failure.*

196. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Interferon – Actimmune Prior Authorization Policy
- Actimmune® (interferon gamma-1b subcutaneous injection – Horizon)

REVIEW DATE: 04/05/2023

OVERVIEW

Actimmune, an interferon gamma, is indicated for the following uses:[1]
- **Chronic granulomatous disease** (CGD), to reduce the frequency and severity of serious infections.
- **Severe, malignant osteopetrosis** (SMO), to delay time to disease progression.

In both disorders, the exact mechanism(s) by which Actimmune has a treatment effect has not been established. Changes in superoxide levels during Actimmune therapy do not predict efficacy and should not be used to assess patient response to therapy.

Disease Overview

Chronic Granulomatous Disease (CGD)

CGD, a primary immune deficiency disease, is caused by defects in the nicotinamide adenine dinucleotide phosphate (NAPDH) oxidase (NOX) enzyme.[2,3] This enzyme is needed by phagocytes (a type of white blood cell) to kill certain types of bacteria and fungi. Patients with CGD are at risk of contracting recurrent and sometimes severe bacterial or fungal infections. Patients may need lifelong regimens of antibiotics and antifungals to prevent infections and use of Actimmune may also help reduce the number of severe infections. Mutations in one of five different genes that encode components of the NADPH (*CYBA, CYBB, NCF1, NCF2*, or *NCF4*) cause CGD. Some patients with CGD do not have an identified mutation in any of these genes and the cause of the condition in these individuals is unknown.

The American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology have jointly accepted responsibility for establishing the practice parameter for the diagnosis and management of primary immunodeficiency.[4] The practice parameter (2015) recommends patients with CGD be given antibacterial and antifungal prophylaxis and Actimmune.

Severe, Malignant Osteopetrosis (SMO)

SMO is an inherited disorder characterized by osteoclast defect and deficient phagocyte oxidative metabolism.[1] There is a reduction in osteoclastic bone reabsorption, which results in bone density overgrowth and poor structural integrity (i.e., bones are more brittle and susceptible to fracture).[5,6] In some cases, this is also accompanied by skeletal abnormalities.[5] The cause of SMO is unknown in some patients, however, variants in one of the following genes have been found to be associated with osteopetrosis: *CA2, CLCN7, IKBLG, ITGB3, LRP5, OSTM1, PLEKHM1, SNX10, TCIRG1, TNFRSF11A, TNFSF11*. The Osteopetrosis Working Group developed expert consensus guidelines for the diagnosis and management of osteopetrosis (2017).[7] The guidelines recommend determination of diagnosis by classic radiographic (X-ray) features of osteopetrosis followed up by genetic testing to differentiate between the different forms of osteopetrosis with unique complications. The guidelines suggest the use of Actimmune to be considered experimental in non-infantile osteopetrosis with limited clinical experience. Furthermore, the guidelines acknowledge the FDA indication for SMO and advise that the indication pertains only to severe infantile osteopetrosis.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Actimmune. Because of the specialized skills required for evaluation and diagnosis of patients treated with Actimmune as well as the monitoring required for adverse events and long-term efficacy, approval requires Actimmune to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Actimmune is recommended in those who meet one of the following criteria:

FDA-Approved Indications

140. Chronic Granulomatous Disease. Approve for 1 year if the patient meets both of the following criteria (A and B):

A) Diagnosis has been established by a molecular genetic test identifying a gene-related mutation linked to chronic granulomatous disease; AND
Note: Examples of gene-related mutations linked to chronic granulomatous disease include biallelic pathogenic variants in *CYBA*, *CYBB*, *NCF1*, *NCF2*, and *NCF4*.

B) The medication is prescribed by or in consultation with an immunologist.

141. Malignant Osteopetrosis, Severe Infantile. Approve for 1 year if the patient meets both of the following criteria (A and B):

A) Diagnosis has been established by ONE of the following (i or ii):

i. Patient has had radiographic (X-ray) imaging demonstrating skeletal features related to osteopetrosis; OR

ii. Patient has had a molecular genetic test identifying a gene-related mutation linked to severe, infantile malignant osteopetrosis; AND
Note: Examples of genes linked to osteopetrosis include *CA2*, *CLCN7*, *IKBLG*, *ITGB3*, *LRP5*, *OSTM1*, *PLEKHM1*, *SNX10*, *TCIRG1*, *TNFRSF11A*, and *TNFSF11*.

B) The medication is prescribed by or in consultation with an endocrinologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Actimmune is not recommended in the following situations:

44. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Iron Replacement – Feraheme Prior Authorization Policy
- Feraheme® (ferumoxytol intravenous infusion – AMAG)

REVIEW DATE: 12/14/2022

OVERVIEW

Feraheme, an iron replacement product, is indicated for the **treatment of iron deficiency anemia** in patients ≥ 18 years of age for the following uses:[1]

- **Chronic kidney disease** (CKD).
- **Intolerance to oral iron or have had unsatisfactory response to oral iron**.

Guidelines

The Kidney Disease: Improving Global Outcomes guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[2] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of intravenous (IV) iron (or in non-dialysis patients with CKD, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in hemoglobin (Hb) concentration without starting ESA treatment is desired and transferrin saturation (TSAT) is ≤ 30% and ferritin is ≤ 500 ng/mL. For adults with CKD on ESA therapy who are not receiving iron supplementation, a trial of IV iron (or in non-dialysis CKD patients, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration or a decrease in ESA dose is desired and TSAT is ≤ 30% and ferritin is ≤ 500 ng/mL. For all pediatric patients with CKD with anemia not on iron or ESA therapy, oral iron (or IV iron in patients receiving hemodialysis) is recommended when TSAT is ≤ 20% and ferritin is ≤ 100 ng/mL. For all pediatric patients with CKD who are receiving ESA therapy but not receiving iron supplementation, it is recommended to administer oral iron (or IV iron for patients receiving hemodialysis) to maintain TSAT > 20% and ferritin > 100 ng/dL.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 1.2023 – December 2, 2022) discuss the management of cancer- and chemotherapy-induced anemia.[3] IV iron therapy is considered an option for patients with absolute iron deficiency (ferritin < 30 ng/mL and TSAT < 20%), functional iron deficiency (ferritin = 30 to 500 ng/mL and TSAT < 50%), and possible functional iron deficiency (ferritin = 501 to 800 ng/mL and TSAT < 50%).

A 2017 focused update of the 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of heart failure states that in patients with New York Heart Association class II or III heart failure, absolute iron deficiency (ferritin < 100 ng/mL) or functional iron deficiency (ferritin = 100 to 300 mg/mL if transferring saturation is < 20%), and with or without anemia, IV iron replacement may be reasonable to improve function status and quality of life.[4] Benefits noted with IV iron therapies included improvements in the six-minute walk test and improved functional capacity.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Feraheme. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Feraheme as well as the monitoring required for adverse events and long-term efficacy, particular approvals require Feraheme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Feraheme is recommended in those who meet one of the following criteria:

FDA-Approved Indications

5. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis**. Approve for 3 years.

6. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis**. Approve for 1 year if the patient meets the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Feraheme is prescribed by or in consultation with a nephrologist or hematologist.

7. **Iron Deficiency Anemia, Other.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets one of the following (i, ii, iii, or iv):
      i. Patient meets both of the following (a and b):
         a) Patient has tried oral iron supplementation; AND
         b) According to the prescriber, oral iron supplementation was ineffective or intolerable; OR
      ii. Patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR
      iii. Patient is currently receiving an erythroid stimulating agent; OR
      Note: Examples of erythroid stimulating agents include an epoetin alfa product, a darbepoetin alfa product, or a methoxy polyethylene glycol-epoetin beta product.
      iv. The medication is being requested for cancer- or chemotherapy-related anemia.

Other Uses with Supportive Evidence

8. **Iron Deficiency Associated with Heart Failure.** Approve for 1 year if the patient meets the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Feraheme is being prescribed by or in consultation with a cardiologist or hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Feraheme is not recommended in the following situations:

197. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Iron Replacement – Ferrlecit Prior Authorization Policy

- Ferrlecit® (sodium ferric gluconate complex in sucrose intravenous infusion – sanofi-aventis)

REVIEW DATE: 12/14/2022

OVERVIEW

Ferrlecit, an iron replacement product, is indicated for the **treatment of iron deficiency anemia** in patients ≥ 6 years of age with **chronic kidney disease** (CKD) **receiving hemodialysis** who are receiving supplemental epoetin therapy.[1]

Guidelines

The Kidney Disease: Improving Global Outcomes guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[2] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of intravenous (IV) iron (or in non-dialysis patients with CKD, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in hemoglobin (Hb) concentration without starting ESA treatment is desired and transferrin saturation (TSAT) is ≤ 30% and ferritin is ≤ 500 ng/mL. For adults with CKD on ESA therapy who are not receiving iron supplementation, a trial of IV iron (or in non-dialysis CKD patients, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration or a decrease in ESA dose is desired and TSAT is ≤ 30% and ferritin is ≤ 500 ng/mL. For all pediatric patients with CKD with anemia not on iron or ESA therapy, oral iron (or IV iron in patients receiving hemodialysis) is recommended when TSAT is ≤ 20% and ferritin is ≤ 100 ng/mL. For all pediatric patients with CKD who are receiving ESA therapy but not receiving iron supplementation, it is recommended to administer oral iron (or IV iron for patients receiving hemodialysis) to maintain TSAT > 20% and ferritin > 100 ng/dL.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 1.2023 – December 2, 2022) discuss the management of cancer- and chemotherapy-induced anemia.[3] IV iron therapy is considered an option for patients with absolute iron deficiency (ferritin < 30 ng/mL and TSAT < 20%), functional iron deficiency (ferritin = 30 to 500 ng/mL and TSAT < 50%), and possible functional iron deficiency (ferritin = 501 to 800 ng/mL and TSAT < 50%).

A 2017 focused update of the 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of heart failure states that in patients with New York Heart Association class II or III heart failure, absolute iron deficiency (ferritin < 100 ng/mL) or functional iron deficiency (ferritin = 100 to 300 mg/mL if transferring saturation is < 20%), and with or without anemia, IV iron replacement may be reasonable to improve function status and quality of life.[4] Benefits noted with IV iron therapies included improvements in the six-minute walk test and improved functional capacity.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Ferrlecit. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ferrlecit as well as the monitoring required for adverse events and long-term efficacy, particular approvals require Ferrlecit to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Ferrlecit is recommended in those who meet one of the following criteria:

FDA-Approved Indication

9. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis**. Approve for 3 years.

Other Uses with Supportive Evidence

10. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis**. Approve for 1 year if the patient meets the following criteria (A and B):
    C) Patient is ≥ 6 years of age; AND
    D) Ferrlecit is prescribed by or in consultation with a nephrologist or hematologist.

11. **Iron Deficiency Anemia, Other.** Approve for 1 year if the patient meets the following (A and B):
    C) Patient is ≥ 6 years of age; AND
    D) Patient meets one of the following (i, ii, iii, or iv):
        i. Patient meets both of the following (a and b):
            a) Patient has tried oral iron supplementation; AND
            b) According to the prescriber, oral iron supplementation was ineffective or intolerable; OR
        ii. Patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR
        iii. Patient is currently receiving an erythroid stimulating agent; OR
        Note: Examples of erythroid stimulating agents include an epoetin alfa product, a darbepoetin alfa product, or a methoxy polyethylene glycol-epoetin beta product.
        iv. The medication is being requested for cancer- or chemotherapy-related anemia.

12. **Iron Deficiency Associated with Heart Failure.** Approve for 1 year if the patient meets the following criteria (A and B):
    C) Patient is ≥ 6 years of age; AND
    D) Ferrlecit is being prescribed by or in consultation with a cardiologist or hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ferrlecit is not recommended in the following situations:

198. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Iron Replacement – INFeD Prior Authorization Policy
- INFeD® (iron dextran intravenous or intramuscular injection – Actavis)

REVIEW DATE: 12/14/2022

OVERVIEW

INFeD, an iron replacement product, is indicated for the treatment of patients ≥ 4 months of age with documented **iron deficiency who have intolerance to oral iron or have had an unsatisfactory response to oral iron**.[1]

Guidelines

The Kidney Disease: Improving Global Outcomes guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[2] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of intravenous (IV) iron (or in non-dialysis patients with CKD, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in hemoglobin (Hb) concentration without starting ESA treatment is desired and transferrin saturation (TSAT) is ≤ 30% and ferritin is ≤ 500 ng/mL. For adults with CKD on ESA therapy who are not receiving iron supplementation, a trial of IV iron (or in non-dialysis CKD patients, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration or a decrease in ESA dose is desired and TSAT is ≤ 30% and ferritin is ≤ 500 ng/mL. For all pediatric patients with CKD with anemia not on iron or ESA therapy, oral iron (or IV iron in patients receiving hemodialysis) is recommended when TSAT is ≤ 20% and ferritin is ≤ 100 ng/mL. For all pediatric patients with CKD who are receiving ESA therapy but not receiving iron supplementation, it is recommended to administer oral iron (or IV iron for patients receiving hemodialysis) to maintain TSAT > 20% and ferritin > 100 ng/dL.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 1.2023 – December 2, 2022) discuss the management of cancer- and chemotherapy-induced anemia.[3] IV iron therapy is considered an option for patients with absolute iron deficiency (ferritin < 30 ng/mL and TSAT < 20%), functional iron deficiency (ferritin = 30 to 500 ng/mL and TSAT < 50%), and possible functional iron deficiency (ferritin = 501 to 800 ng/mL and TSAT < 50%).

A 2017 focused update of the 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of heart failure states that in patients with New York Heart Association class II or III heart failure, absolute iron deficiency (ferritin < 100 ng/mL) or functional iron deficiency (ferritin = 100 to 300 mg/mL if transferring saturation is < 20%), and with or without anemia, IV iron replacement may be reasonable to improve function status and quality of life.[4] Benefits noted with IV iron therapies included improvements in the six-minute walk test and improved functional capacity.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of INFeD. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with INFeD as well as the monitoring required for adverse events and long-term efficacy, particular approvals require INFeD to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of INFeD is recommended in those who meet one of the following criteria:

FDA-Approved Indication

13. Iron Deficiency Anemia, Other. Approve for 1 year if the patient meets one of the following (A, B, C, or D):

- **E)** Patient meets both of the following (i and ii):
  - **i.** Patient has tried oral iron supplementation; AND
  - **ii.** According to the prescriber, oral iron supplementation was ineffective or intolerable; OR
- **F)** Patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR
- **G)** Patient is currently receiving an erythroid stimulating agent; OR
  Note: Examples of erythroid stimulating agents include an epoetin alfa product, a darbepoetin alfa product, or a methoxy polyethylene glycol-epoetin beta product.
- **H)** The medication is being requested for cancer- or chemotherapy-related anemia.

Other Uses with Supportive Evidence

14. Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis. Approve for 3 years.

15. Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis. Approve for 1 year if the medication is prescribed by or in consultation with a nephrologist or hematologist.

16. Iron Deficiency Associated with Heart Failure. Approve for 1 year if the medication is being prescribed by or in consultation with a cardiologist or hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of INFeD is not recommended in the following situations:

199. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

62. INFeD® [prescribing information]. Parsippany, NJ: Actavis; April 2021.
63. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int.* 2012;2(Suppl):279-335.
64. The NCCN Hematopoietic Growth Factors Guidelines in Oncology (version 1.2023 – December 2, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org/clinical.asp. Accessed on December 9, 2022.
65. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure. *J Am Coll Cardiol.* 2017;70(6):776-803.

PRIOR AUTHORIZATION POLICY

POLICY: Iron Replacement – Injectafer Prior Authorization Policy

- Injectafer® (ferric carboxymaltose intravenous infusion or slow injection – American Regent)

REVIEW DATE: 12/14/2022

OVERVIEW

Injectafer, an iron replacement product, is indicated for the treatment of:[1]

- **Iron deficiency anemia (IDA)**, in patients ≥ 1 year of age, with either an **intolerance or unsatisfactory response to oral iron**.
- **IDA,** in patients ≥ 18 years of age, with **non-dialysis dependent chronic kidney disease** (CKD).
- **Iron deficiency**, in patients ≥ 18 years of age, with **heart failure** and New York Heart Association class II/III to improve exercise capacity.

Guidelines

The Kidney Disease: Improving Global Outcomes guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[2] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of intravenous (IV) iron (or in non-dialysis patients with CKD, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in hemoglobin (Hb) concentration without starting ESA treatment is desired and transferrin saturation (TSAT) is ≤ 30% and ferritin is ≤ 500 ng/mL. For adults with CKD on ESA therapy who are not receiving iron supplementation, a trial of IV iron (or in non-dialysis CKD patients, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration or a decrease in ESA dose is desired and TSAT is ≤ 30% and ferritin is ≤ 500 ng/mL. For all pediatric patients with CKD with anemia not on iron or ESA therapy, oral iron (or IV iron in patients receiving hemodialysis) is recommended when TSAT is ≤ 20% and ferritin is ≤ 100 ng/mL. For all pediatric patients with CKD who are receiving ESA therapy but not receiving iron supplementation, it is recommended to administer oral iron (or IV iron for patients receiving hemodialysis) to maintain TSAT > 20% and ferritin > 100 ng/dL.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 2.2023 – March 6, 2023) discuss the management of cancer- and chemotherapy-induced anemia.[3] IV iron therapy is considered an option for patients with absolute iron deficiency (ferritin < 30 ng/mL and TSAT < 20%), functional iron deficiency (ferritin = 30 to 500 ng/mL and TSAT < 50%), and possible functional iron deficiency (ferritin = 501 to 800 ng/mL and TSAT < 50%).

A 2017 focused update of the 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of heart failure states that in patients with New York Heart Association class II or III heart failure, absolute iron deficiency (ferritin < 100 ng/mL) or functional iron deficiency (ferritin = 100 to 300 mg/mL if transferring saturation is < 20%), and with or without anemia, IV iron replacement may be reasonable to improve function status and quality of life.[4] Benefits noted with IV iron therapies included improvements in the six-minute walk test and improved functional capacity.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Injectafer. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Injectafer as well as the monitoring required for adverse events and long-term efficacy, particular approvals require Injectafer to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Injectafer is recommended in those who meet the following criteria:

FDA-Approved Indications

17. Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are NOT on Dialysis. Approve for 1 year if the patient meets the following (A and B):
- **E)** Patient is ≥ 18 years of age; AND
- **F)** Injectafer is prescribed by or in consultation with a nephrologist or hematologist.

18. Iron Deficiency Anemia, Other. Approve for 1 year if the patient meets the following (A and B):
- **I)** Patient is ≥ 1 year of age; AND
- **J)** Patient meets one of the following (i, ii, iii, or iv):
  - **i.** Patient meets both of the following (a and b):
    - **a)** Patient has tried oral iron supplementation; AND
    - **b)** According to the prescriber, oral iron supplementation was ineffective or intolerable; OR
  - **ii.** Patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR
  - **iii.** Patient is currently receiving an erythroid stimulating agent; OR
    Note: Examples of erythroid stimulating agents include an epoetin alfa product, a darbepoetin alfa product, or a methoxy polyethylene glycol-epoetin beta product.
  - **iv.** The medication is being requested for cancer- or chemotherapy-related anemia.

19. Iron Deficiency Associated with Heart Failure. Approve for 1 year if the patient meets the following (A and B):
- **E)** Patient is ≥ 18 years of age; AND
- **F)** Injectafer is being prescribed by or in consultation with a cardiologist or hematologist.

Other Uses with Supportive Evidence

20. Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis. Approve for 3 years.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Injectafer is not recommended in the following situations:

200. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

66. Injectafer® [prescribing information]. Shirley, NY: American Regent; May 2023.
67. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int.* 2012;2(Suppl):279-335.
68. The NCCN Hematopoietic Growth Factors Guidelines in Oncology (version 2.2023 – March 6, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org Accessed on July 25, 2023.
69. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure. *J Am Coll Cardiol.* 2017;70(6):776-803.

PRIOR AUTHORIZATION POLICY

POLICY: Iron Replacement – Monoferric Prior Authorization Policy
- Monoferric® (ferric derisomaltose intravenous infusion – Pharmacosmos)

REVIEW DATE: 12/14/2022

OVERVIEW

Monoferric, an iron replacement product, is indicated for the **treatment of iron deficiency anemia** in patients ≥ 18 years of age for the following uses:[1]

- **Intolerance to oral iron or have had unsatisfactory response to oral iron**.
- **Non-hemodialysis chronic kidney disease** (CKD).

Guidelines

The Kidney Disease: Improving Global Outcomes guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[2] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of intravenous (IV) iron (or in non-dialysis patients with CKD, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in hemoglobin (Hb) concentration without starting ESA treatment is desired and transferrin saturation (TSAT) is ≤ 30% and ferritin is ≤ 500 ng/mL. For adults with CKD on ESA therapy who are not receiving iron supplementation, a trial of IV iron (or in non-dialysis CKD patients, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration or a decrease in ESA dose is desired and TSAT is ≤ 30% and ferritin is ≤ 500 ng/mL. For all pediatric patients with CKD with anemia not on iron or ESA therapy, oral iron (or IV iron in patients receiving hemodialysis) is recommended when TSAT is ≤ 20% and ferritin is ≤ 100 ng/mL. For all pediatric patients with CKD who are receiving ESA therapy but not receiving iron supplementation, it is recommended to administer oral iron (or IV iron for patients receiving hemodialysis) to maintain TSAT > 20% and ferritin > 100 ng/dL.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 1.2023 – December 2, 2022) discuss the management of cancer- and chemotherapy-induced anemia.[3] IV iron therapy is considered an option for patients with absolute iron deficiency (ferritin < 30 ng/mL and TSAT < 20%), functional iron deficiency (ferritin = 30 to 500 ng/mL and TSAT < 50%), and possible functional iron deficiency (ferritin = 501 to 800 ng/mL and TSAT < 50%).

A 2017 focused update of the 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of heart failure states that in patients with New York Heart Association class II or III heart failure, absolute iron deficiency (ferritin < 100 ng/mL) or functional iron deficiency (ferritin = 100 to 300 mg/mL if transferring saturation is < 20%), and with or without anemia, IV iron replacement may be reasonable to improve function status and quality of life.[4] Benefits noted with IV iron therapies included improvements in the six-minute walk test and improved functional capacity.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Monoferric. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Monoferric as well as the monitoring required for adverse events and long-term efficacy, particular approvals require Monoferric to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Monoferric is recommended in those who meet one of the following criteria:

FDA-Approved Indications

21. Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis. Approve for 1 year if the patient meets the following criteria (A and B):
- **G)** Patient is ≥ 18 years of age; AND
- **H)** Monoferric is prescribed by or in consultation with a nephrologist or hematologist.

22. Iron Deficiency Anemia, Other. Approve for 1 year if the patient meets the following (A and B):
- **K)** Patient is ≥ 18 years of age; AND
- **L)** Patient meets one of the following (i, ii, iii, or iv):
  - **i.** Patient meets both of the following (a and b):
    - **a)** Patient has tried oral iron supplementation; AND
    - **b)** According to the prescriber, oral iron supplementation was ineffective or intolerable; OR
  - **ii.** Patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR
  - **iii.** Patient is currently receiving an erythroid stimulating agent; OR
    Note: Examples of erythroid stimulating agents include an epoetin alfa product, a darbepoetin alfa product, or a methoxy polyethylene glycol-epoetin beta product.
  - **iv.** The medication is being requested for cancer- or chemotherapy-related anemia.

Other Uses with Supportive Evidence

23. Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis. Approve for 3 years.

24. Iron Deficiency Associated with Heart Failure. Approve for 1 year if the patient meets the following criteria (A and B):
- **G)** Patient is ≥ 18 years of age; AND
- **H)** Monoferric is being prescribed by or in consultation with a cardiologist or hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Monoferric is not recommended in the following situations:

201. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

70. Monoferric® intravenous infusion [prescribing information]. Holbaek, Denmark: Pharmacosmos; August 2022.
71. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int*. 2012;2(Suppl):279-335.
72. The NCCN Hematopoietic Growth Factors Guidelines in Oncology (version 1.2023 – December 2, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 9, 2022.
73. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure. *J Am Coll Cardiol*. 2017;70(6):776-803.

PRIOR AUTHORIZATION POLICY

POLICY: Iron Replacement – Venofer Prior Authorization Policy

- Venofer® (iron sucrose intravenous infusion or slow injection – American Regent)

REVIEW DATE: 12/14/2022

OVERVIEW

Venofer, an iron replacement product, is indicated for the treatment of **iron deficiency anemia in patients with chronic kidney disease** (CKD).[1]

Guidelines

The Kidney Disease: Improving Global Outcomes guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[2] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of intravenous (IV) iron (or in non-dialysis patients with CKD, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in hemoglobin (Hb) concentration without starting ESA treatment is desired and transferrin saturation (TSAT) is ≤ 30% and ferritin is ≤ 500 ng/mL. For adults with CKD on ESA therapy who are not receiving iron supplementation, a trial of IV iron (or in non-dialysis CKD patients, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration or a decrease in ESA dose is desired and TSAT is ≤ 30% and ferritin is ≤ 500 ng/mL. For all pediatric patients with CKD with anemia not on iron or ESA therapy, oral iron (or IV iron in patients receiving hemodialysis) is recommended when TSAT is ≤ 20% and ferritin is ≤ 100 ng/mL. For all pediatric patients with CKD who are receiving ESA therapy but not receiving iron supplementation, it is recommended to administer oral iron (or IV iron for patients receiving hemodialysis) to maintain TSAT > 20% and ferritin > 100 ng/dL.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 1.2023 – December 2, 2022) discuss the management of cancer- and chemotherapy-induced anemia.[3] IV iron therapy is considered an option for patients with absolute iron deficiency (ferritin < 30 ng/mL and TSAT < 20%), functional iron deficiency (ferritin = 30 to 500 ng/mL and TSAT < 50%), and possible functional iron deficiency (ferritin = 501 to 800 ng/mL and TSAT < 50%).

A 2017 focused update of the 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of heart failure states that in patients with New York Heart Association class II or III heart failure, absolute iron deficiency (ferritin < 100 ng/mL) or functional iron deficiency (ferritin = 100 to 300 mg/mL if transferring saturation is < 20%), and with or without anemia, IV iron replacement may be reasonable to improve function status and quality of life.[4] Benefits noted with IV iron therapies included improvements in the six-minute walk test and improved functional capacity.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Venofer. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Venofer as well as the monitoring required for adverse events and long-term efficacy, particular approvals require Venofer to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Venofer is recommended in those who meet one of the following criteria:

FDA-Approved Indications

25. Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis. Approve for 3 years.

26. Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis. Approve for 1 year if the medication is prescribed by or in consultation with a nephrologist or hematologist.

Other Uses with Supportive Evidence

27. Iron Deficiency Anemia, Other. Approve for 1 year if the patient meets one of the following (A, B, C, or D):

M) Patient meets both of the following (i and ii):
- **i.** Patient has tried oral iron supplementation; AND
- **ii.** According to the prescriber, oral iron supplementation was ineffective or intolerable; OR

N) Patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR

O) Patient is currently receiving an erythroid stimulating agent; OR
Note: Examples of erythroid stimulating agents include an epoetin alfa product, a darbepoetin alfa product, or a methoxy polyethylene glycol-epoetin beta product.

P) The medication is being requested for cancer- or chemotherapy-related anemia.

28. Iron Deficiency Associated with Heart Failure. Approve for 1 year if the medication is being prescribed by or in consultation with a cardiologist or hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Venofer is not recommended in the following situations:

202. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

74. Venofer® intravenous infusion or slow injection [prescribing information]. Shirley, NY: American Regent; July 2022.
75. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int.* 2012;2(Suppl):279-335.
76. The NCCN Hematopoietic Growth Factors Guidelines in Oncology (version 1.2023 – December 2, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 9, 2022.
77. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure. *J Am Coll Cardiol.* 2017;70(6):776-803.

PRIOR AUTHORIZATION POLICY

POLICY: Lidocaine Patch Products Prior Authorization Policy
- Lidoderm® (lidocaine 5% patch – Endo, generic)
- ZTlido® (lidocaine 1.8% topical system – Scilex)

REVIEW DATE: 09/27/2023

OVERVIEW

Lidocaine 5% patch and ZTlido are indicated for the **relief of pain associated with postherpetic neuralgia** (PHN).[1,2]

Lidocaine is an amide-type local anesthetic agent whose neuronal membrane stabilizing effect produces a local analgesic effect when applied transdermally.[1,2] The lidocaine penetration into intact skin is adequate to produce an analgesic effect, but less than the amount needed to produce a complete sensory block. In a single-dose, crossover study in healthy volunteers, ZTlido demonstrated equivalent exposure and peak concentration of lidocaine to lidocaine patch 5% (Lidoderm, generics).[2]

Other Uses with Supportive Evidence

Lidocaine 5% patches have been shown to be effective in treating low back pain in open-label studies in patients not achieving adequate pain relief despite as needed or stable doses of non-selective nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, gabapentin, tramadol, or opioids.[3-5] The guidelines for treatment of low back pain (2017) do not address the use of topical lidocaine; however, various other agents are used for pain associated with low back pain.[6] In patients with acute or subacute low back pain, the guidelines recommend NSAIDs or skeletal muscle relaxants as pharmacologic treatment options (strong recommendation; moderate-quality evidence). In patients with chronic low back pain who have had an inadequate response to nonpharmacologic therapy, the guidelines recommend consideration of pharmacologic treatment with NSAIDs as first-line therapy or tramadol or duloxetine as second-line therapy. Of note, tramadol is a narcotic and, like other opioids, is associated with the risk for abuse. Clinicians should only consider opioids as an option in patients who have failed the aforementioned treatments and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients (weak recommendation; moderate-quality evidence). Moderate-quality evidence showed no difference in pain between tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors vs. placebo, and low-quality evidence showed no differences in function for antidepressants. Moderate-quality evidence showed that duloxetine was associated with a small improvement in pain intensity and function vs. placebo.

Lidocaine 5% patch has been shown to be effective in treating neuropathic pain of various forms and etiologies as monotherapy and, more commonly, as adjunctive therapy to a stable analgesic regimen.[3,7-14] There is evidence to suggest that lidocaine 5% patch, along with several other analgesics (i.e., opioids, tramadol, TCAs), can be effective as first-line therapy in the management of neuropathic pain.[12] The 2011 evidence-based guideline on treatment of painful diabetic neuropathy, published by the American Academy of Neurology (AAN), indicates the lidocaine 5% patch may be considered for the treatment of painful diabetic neuropathy.[15] Recommendations for the pharmacological management of neuropathic pain, published by the Mayo Foundation, indicate that lidocaine 5% patch has shown efficacy in patients with varying types of neuropathic pain, and are considered a first-line therapy.[16]

Several open-label trials have shown lidocaine 5% patches to be effective in treating pain associated with osteoarthritis of the knee both as monotherapy and in combination with other analgesics (e.g., NSAIDs, COX-2 inhibitors, opioids, tramadol, acetaminophen).[17-20] In one open-label comparative trial (prematurely terminated before enrollment goals were achieved due to safety concerns surrounding the entire COX-2 class),[21] treatment of knee osteoarthritis with lidocaine 5% patches (1-⅓ patches applied every 24 hours) resulted in comparable reductions in pain intensity scores as celecoxib 200 mg/day.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of lidocaine patches. All approvals are provided for the duration noted below.

Automation: When available, the ICD-10 codes for postherpetic polyneuropathy (B02.23) will be used as part of automation to allow approval of the requested medication.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of lidocaine patches is recommended in those who meet one of the following:

FDA-Approved Indication

1. **Postherpetic Neuralgia (PHN).** Approve for 1 year.

Other Uses with Supportive Evidence

2. **Low Back Pain.** Approve for 1 year after trying at least three pharmacologic therapies with each one from a different class of medication used to treat low back pain.
   Note: Examples of different classes of pharmacologic therapies for low back pain include acetaminophen, nonsteroidal anti-inflammatory drugs, muscle relaxants, celecoxib, duloxetine, gabapentin. Examples of nonsteroidal anti-inflammatory drugs include etodolac, meloxicam, and nabumetone. Examples of muscle relaxants include carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, and orphenadrine.

3. **Neuropathic Pain.** Approve for 1 year.
   Note: For neuropathic pain due to radiculopathy or sciatica, please refer to the Not Recommended for Approval section for Radiculopathy or Sciatica.

4. **Osteoarthritis.** Approve for 1 year after trying at least three pharmacologic therapies with each one from a different class of medication used for the treatment of osteoarthritis.
   Note: Examples of different classes of pharmacologic therapies for osteoarthritis include acetaminophen, celecoxib, nonsteroidal anti-inflammatory drugs, salicylates, intraarticular glucocorticoids, intraarticular hyaluronan, topical capsaicin, and topical methylsalicylate.[22] Examples of nonsteroidal anti-inflammatory drugs include etodolac, meloxicam, and nabumetone.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of lidocaine patches is not recommended in the following situations:

45. **Carpal Tunnel Syndrome.** Two open-label trials have investigated the lidocaine 5% patch for the relief of pain associated with carpal tunnel symdrome.[23,24] In an open-label, parallel-group, single-center, active-controlled trial,[23] 40 patients with carpal tunnel syndrome were randomized to daily treatment with lidocaine patch 5% or an injection of lidocaine 1% plus methylprednisolone. After 4 weeks of treatment, both groups reported statistically significant improvement in pain scores. A 6-week, randomized, parallel-group, open-label multicenter study[24] found that lidocaine 5% patches given every 24 hours and naproxen 500 mg twice daily both led to significant reductions is the Average Pain Intensity scores in 100 patients with carpal tunnel syndrome. The 2016 American Academy of Orthopaedic Surgeons (AAOS) guidelines on carpal tunnel syndrome do not mention topical lidocaine in their recommendations for treatment.[25] In addition, the AAOS guidelines have a supplemental evidence table that addresses the studies AAOS evaluated for their guidelines. This table states that the above-referenced articles were excluded from their guidelines because they used non-validated outcome measures.

46. **Fibromyalgia.** There are no data available on the use of lidocaine patches in treating pain associated with fibromyalgia.

47. **Myofascial Pain as Adjunctive Therapy.** Published data are limited to small ($n \leq 60$ in each study) studies of lidocaine 5% patches.[26-29] Larger, controlled studies are needed to fully determine the place in therapy of lidocaine patches for the treatment of myofascial pain.

48. **Pain Associated with Rib Fractures.** Lidocaine 5% patch did not significantly improve pain control in patients with traumatic rib fractures in one randomized, double-blind, placebo-controlled study.[30] A retrospective chart analysis found lidocaine patches decreased pain scores in 29 patients with rib fractures vs. 29 matched controls, with no change in narcotic use and no difference in time to return to baseline activity.[31] A small (n = 44) double-blind, placebo-controlled study in hospitalized patients with traumatic rib fracture in Taiwan found that lidocaine 5% patch decreased pain scores after Day 5 of therapy vs. placebo, with no difference in oral opioid use but decreased meperidine injection use.[32] Larger, controlled studies are needed to fully determine the place in therapy of lidocaine 5% patch for the treatment of pain associated with rib fractures.

49. **Radiculopathy.** Published data on the use of lidocaine patches in treating pain associated with radiculopathy is limited.[11,33] Larger, controlled studies are needed to fully determine the place in therapy of lidocaine patches for the treatment of radiculopathy.

50. **Rheumatoid Arthritis (RA).** There are no data available on the use of lidocaine patches in treating pain associated with RA.

51. **Sciatica.** There are no data available on the use of lidocaine patches in treating pain associated with sciatica.

52. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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124. Lidoderm® patches [prescribing information]. Malvern, PA: Endo; November 2022.
125. ZTlido® transdermal system [prescribing information]. San Diego, CA: Scilex; April 2021.
126. White WT, Patel N, Drass M, Nalamachu S. Lidocaine patch 5% with systemic analgesics such as gabapentin: a rational polypharmacy approach for the treatment of chronic pain. *Pain Med*. 2003;4(4):321-30.
127. Galer BS, Gammaitoni AR, Oleka N, Jensen MP, Argoff CE. Use of the lidocaine patch 5% in reducing intensity of various pain qualities reported by patients with low-back pain. *Curr Med Res Opin*. 2004;20(Suppl 2):S5-12.
128. Gimbel J, Linn R, Hale M, Nicholson B. Lidocaine patch treatment in patients with low back pain: results of an open-label, nonrandomized pilot study. *Am J Ther*. 2005;12:311-319.
129. Qaseem A, Wilt TJ, McLean RM, et al. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2017;166(7):514-530.
130. Barbano RL, Herrmann DN, Hart-Gouleau S, Pennella-Vaughan J, Lodewick PA, Dworkin RH. Effectiveness, tolerability, and impact on quality of life of the 5% lidocaine patch in diabetic polyneuropathy. *Arch Neurol*. 2004;61(6):914-918.
131. IBM Micromedex®. 2023 IBM Corporation. Available at: http://www.micromedexsolutions.com/home/dispatch. Accessed on September 25, 2023. Search terms: lidocaine.
132. Meier T, Wasner G, Faust M, et al. Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study. *Pain*. 2003;106(1-2):151-158.
133. Galer BS, Jensen MP, Ma T, et al. The lidocaine patch 5% effectively treats all neuropathic pain qualities: results of a randomized, double-blind, vehicle-controlled, three-week efficacy study with use of the neuropathic pain scale. *Clin J Pain*. 2002;18:297-301.
134. Devers A, Galer BS. Topical lidocaine patch relieves a variety of neuropathic pain conditions: an open-label study. *Clin J Pain*. 2000;16:205-208.
135. Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch Neurol*. 2003;60(11):1524-1534.
136. Herrmann DN, Barbano RL, Hart-Gouleau S, et al. An open-label study of the lidocaine patch 5% in painful idiopathic sensory polyneuropathy. *Am Acad Pain Med*. 2005;6(5):379-384.
137. Fleming JA, O'Connor BD. Use of lidocaine patches for neuropathic pain in a comprehensive cancer centre. *Pain Res Manage*. 2009;14:381-388.
138. Bril V, England J, Franklin GM, et al. Evidence-based Guideline: Treatment of Painful Diabetic Neuropathy Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology*. 2011;76(20):1758-1765.
139. Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc*. 2010;85:S3-S14.
140. Galer BS, Sheldon E, Patel N, et al. Topical lidocaine patch 5% may target a novel underlying pain mechanism in osteoarthritis. *Curr Med Res Opin*. 2004;20(9):1455-1458.
141. Gammaitoni AR, Galer BS, Onawala R, et al. Lidocaine patch 5% and its positive impact on pain qualities in osteoarthritis: results of a pilot 2-week, open-label study using the Neuropathic Pain Scale. *Curr Med Res Opin*. 2004;20(Suppl 2):S13-19.
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PRIOR AUTHORIZATION POLICY

POLICY: Lipodystrophy – Egrifta Prior Authorization Policy
- Egrifta SV® (tesamorelin subcutaneous injection – Theratechnologies)

REVIEW DATE: 05/31/2023

OVERVIEW

Egrifta SV, an analog of human growth hormone-releasing factor, is indicated for the reduction of excess abdominal fat in patients with **human immunodeficiency virus (HIV) who have lipodystrophy**.[1,3]

Limitations of use: 1) Long-term cardiovascular safety of Egrifta SV has not been established. 2) Not indicated for weight loss management. 3) There are no data to support improved compliance with anti-retroviral therapies in HIV-positive patients taking Egrifta SV. In the pivotal trial, all patients had lipodystrophy and excess abdominal fat, evidenced by a waist circumference ≥ 95 cm (≥ 94 cm for women) and a waist-to-hip ratio ≥ 0.94 (≥ 0.88 for women).[1] Patients were required to be on a stable antiretroviral regimen for at least 8 weeks. Safety and effectiveness of Egrifta SV have been established in patients between 18 and 65 years of age.

Disease Overview

Lipodystrophy is the change in body fat which affects some patients with HIV infection, either due to HIV infection or due to medications to treat HIV.[2] Lipodystrophy is not a concern for most people who start HIV treatment now, because newer HIV medications are less likely to cause this effect.

Safety

Because the long-term cardiovascular safety and potential long-term cardiovascular benefit are not established, careful consideration should be given whether to continue Egrifta SV treatment in patients who do not show a clear efficacy response, as judged by the degree of reduction in visceral adipose tissue measured by waist circumference or computerized tomography scan. In the pivotal studies, efficacy of Egrifta SV was assessed at Week 26. Because Egrifta SV induces the release of endogenous growth hormone (a known growth factor) and increases serum IGF-1, the benefits of treatment should be weighed against the increased risk of malignancies patients who are HIV-positive. Since the effect of prolonged IGF-1 elevations on the development or progression of malignancies is unknown, monitor IGF-1 levels closely during Egrifta SV therapy and consider discontinuation in patients with persistent elevations of IGF-1 levels (e.g., > 3 standard deviation scores), especially if the patient has not experienced a robust response. Egrifta SV should be used with caution in patients who develop glucose intolerance or diabetes; discontinuation of therapy should be considered for patients who do not show a clear efficacy response.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Egrifta SV. Because of the specialized skills required for evaluation and diagnosis of patients treated with Egrifta SV as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Egrifta SV to be prescribed by or in consultation with a physician who specializes in the condition being treated. In the approval indication, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression. All approvals are provided for the duration noted below. When approvals are authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Egrifta SV is recommended in those who meet the following criteria:

FDA-Approved Indication

D) Lipodystrophy Associated with Human Immunodeficiency Virus (HIV) Infection. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):
- **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following criteria (i, ii, iii, iv, and v):
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** The medication is prescribed for the reduction of excess abdominal fat; AND
  - **iii.** Patient meets ONE of the following criteria (a or b):
    - **a)** If male*, waist circumference is ≥ 95 cm (37.4 in) and waist-to-hip ratio is ≥ 0.94; OR
    - **b)** If female*, waist circumference is ≥ 94 cm (37 in) and waist-to-hip ratio is ≥ 0.88; AND
  - **iv.** Patient has been stable on an antiretroviral regimen for at least 8 weeks; AND
    Note: Examples include antiretroviral regimens containing protease inhibitors, nucleoside reverse transcriptase inhibitors, and/or non-nucleoside reverse transcriptase inhibitors.
  - **v.** The medication is prescribed by or in consultation with an endocrinologist or a physician specializing in the treatment of HIV infection (e.g., infectious disease, oncology).
- **B)** Patient is Currently Receiving Egrifta. Approve for 1 year if the patient has responded, as determined by the prescriber.
  Note: Examples of a response include reduction in visceral adipose tissue measured by waist circumference or computed tomography (CT) scan.

***** Refer to the Policy Statement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Egrifta SV is not recommended in the following situations:

53. Abdominal Obesity in a Patient without Human Immunodeficiency Virus (HIV) Infection. More data are needed. Egrifta SV has been studied in a very limited number patients who have abdominal obesity without HIV infection.[4] To be eligible for the published trial, patients were required to have a peak stimulated growth hormone no higher than 9 mcg/L on a standardized growth hormone-releasing hormone-arginine stimulation test. Patients (n = 60) were randomized in a 1:1 ratio to treatment with Egrifta SV 2 mg once daily or placebo. The primary endpoint was the change in visceral adipose tissue from baseline. Over 12 months (using last observation carried forward), visceral adipose tissue improved significantly in patients treated with Egrifta SV compared with placebo (net treatment effect vs. placebo: -35 [95% confidence interval: -58, -12]; P = 0.003). Treatment with Egrifta SV increased IGF-1 by 90%, decreased triglycerides by 20%, and decreased log C-reactive protein by 24% compared with placebo. There was no effect on total cholesterol, high-density lipoprotein cholesterol, or low-density lipoprotein cholesterol in the treatment groups.

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54. Human Immunodeficiency Virus (HIV)-Related Cachexia, Weight Loss, or Fat Distribution other than Lipodystrophy. Egrifta SV has not been studied in these conditions.

55. **Patient is > 65 Years of Age.** There is no information on the use of Egrifta SV in patients greater than 65 years of age with HIV and lipodystrophy.[1]

56. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Lipodystrophy – Myalept Prior Authorization Policy
- Myalept® (metreleptin subcutaneous injection – Aegerion)

REVIEW DATE: 06/14/2023

OVERVIEW

Myalept, a recombinant analog of human leptin, is indicated as an adjunct to diet as replacement therapy to treat complications of leptin deficiency in patients with **congenital or acquired generalized lipodystrophy**.[1]

Limitations of Use: The safety and efficacy of Myalept have not been established for the treatment of complications of partial lipodystrophy, liver disease (including nonalcoholic steatophepatitis [NASH]), human immunodeficiency virus (HIV)-related lipodystrophy, or metabolic disease (including diabetes mellitus and hypertriglyceridemia) without concurrent evidence of generalized lipodystrophy.

Congenital generalized lipodystrophy is an inherited autosomal recessive disease.[21] AGPAT2 and BSCL2 gene mutations responsible for 95% of currently identified cases, while mutations of CAV1 and the PTRF gene have also been reported, although much less frequently. Several patients with congenital generalized lipodystrophy do not have any of the four known gene mutations, indicating that not all mutations associated with congenital generalized lipodystrophy have been identified. Patients with this condition can experience a variety of complications, such as hyperinsulinemia, diabetes mellitus, hypertriglyceridemia, pancreatitis, fatty liver, and loss of subcutaneous adipose tissue.

Guidelines

Guidelines on the diagnosis and management of lipodystrophy syndromes were published in 2016 and endorsed by multiple groups of endocrine experts, including the Endocrine Society, the Pediatric Endocrine Society, the American Diabetes Association, and the American Association of Clinical Endocrinologists.[2] These guidelines note that lipodystrophy is an incurable condition and no treatment will regrow adipose tissue. Myalept is the only drug specifically indicated for the treatment of lipodystrophy. Myalept, along with diet, is recommended as the first-line treatment for metabolic and endocrine abnormalities in patients with generalized lipodystrophy. In children, Myalept may also be used to prevent the development of comorbidities.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Myalept. Because of the specialized skills required for evaluation and diagnosis of patients treated with Myalept, as well as the monitoring required for adverse events and long-term efficacy, approval requires Myalept to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Myalept is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Generalized Lipodystrophy (Congenital or Acquired):** Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, and D):
   - **A)** Patient meets ONE of the following (i or ii):
     - **i.** Patient has **congenital** generalized lipodystrophy and meets ONE of the following criteria (a or b):
       - **a)** Patient has had a genetic test demonstrating one gene mutation (i.e., AGPAT2, BSCL2, CAV1, or PTRF) confirming the diagnosis of congenital generalized lipodystrophy; OR
       - **b)** Patient meets BOTH of the following criteria (1 and 2):
         - **(1)** Patient has had a genetic test that did not demonstrate an AGPAT2, BSCL2, CAV1, or PTRF gene mutation; AND
         - **(2)** A clinical diagnosis of congenital generalized lipodystrophy has been made by a specialist with experience in treating patients with lipodystrophy; OR
     - **ii.** Patient has **acquired** generalized lipodystrophy; AND
   - **B)** Patient has experienced one or more manifestations of leptin deficiency; AND
     Note: Manifestations of leptin deficiency include hyperinsulinemia, type 2 diabetes mellitus, and hypertriglyceridemia.
   - **C)** Myalept will be used in conjunction with dietary modification; AND
   - **D)** Medication is prescribed by, or in consultation with, an endocrinologist or a geneticist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Myalept is not recommended in the following situations:

57. **General Obesity not associated with Congenital Leptin Deficiency.** Myalept is contraindicated in patients with general obesity not associated with congenital leptin deficiency.[1] Myalept was previously evaluated in two clinical development programs for obesity, both as monotherapy (n > 1,100) and in combination with Symlin® (pramlintide acetate for injection; n > 600).[3] Published studies on the effects of leptin therapy in these patients without leptin deficiency yielded conflicting efficacy results.[4,5] The studies involving obese patients (some with type 2 diabetes mellitus), with the exception of one dose-escalation trial, failed to show significant weight loss with Myalept therapy and resulted in clinically insignificant changes in other metabolic parameters, such as insulin sensitivity.[6-10] One additional randomized, double-blind, placebo-controlled crossover study evaluated the efficacy of leptin administration to promote further weight reduction in patients who had undergone Roux-en-Y gastric bypass surgery.[11] Following 16 weeks of therapy, Myalept was not found to promote additional decreases in body weight compared with placebo.

58. **Human Immunodeficiency Virus (HIV)-related Lipodystrophy.** Myalept is not indicated for the treatment of patients with HIV-related lipodystrophy.[1] Results from four small studies of patients with HIV-associated lipodystrophy and leptin deficiency showed mixed results with Myalept therapy.[12-15] One study found significantly improved fasting insulin levels, insulin resistance and high-density lipoprotein (HDL) levels, but no significant differences in fasting glucose levels, free-fatty acid levels, or low-density lipoprotein (LDL) levels when Myalept was compared with placebo.[12] Another demonstrated improved fasting insulin levels, but no difference in intravenous glucose disappearance, fasting serum glucose concentration, glycosylated hemoglobin (HbA_{1C}) levels, body mass index (BMI), or lipid parameters after treatment with Myalept.[13] Two additional studies found that therapy with Myalept improved some, but not all metabolic parameters in patients infected with HIV.[14,15] More

information is needed to determine if Myalept is a safe and effective treatment for HIV-related lipodystrophy.

59. **Partial Lipodystrophy.** The safety and efficacy of Myalept in the treatment of the complications of partial lipodystrophy have not been established.[1] The effects of Myalept therapy in patients with partial lipodystrophy have been evaluated; the pivotal trial of Myalept included a subset of patients (n = 24) with partial lipodystrophy.[16] Overall, patients with partial lipodystrophy had milder baseline metabolic abnormalities than patients with generalized lipodystrophy. Following 12 months of Myalept therapy, patients experienced a reduction in HbA_{1C}, fasting plasma glucose, and fasting triglycerides; however, the magnitude of the improvements was less than those observed in patients with generalized lipodystrophy. There are data showing sustained improvements out to 36 months as well.[17] Additional data also highlight the heterogeneity of partial lipodystrophy; Myalept may provide improvement in some metabolic parameters in certain patients with partial lipodystrophy, but more data are needed to confirm these benefits.[18-20] Current lipodystrophy guidelines (2016) outline certain patients with partial lipodystrophy that may benefit from Myalept therapy, but indicate a lower level of evidence to support use in this patient population compared with generalized lipodystrophy.[2] Myalept prescribing information continues to list partial lipodystrophy as a limitation of use.[1]

60. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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39. PRIOR AUTHORIZATION POLICY

POLICY: Lucemyra Prior Authorization Policy
- Lucemyra® (lofexidine tablets – US WorldMeds)

REVIEW DATE: 07/26/2023

OVERVIEW

Lucemyra, a central alpha-2 adrenergic agonist, is indicated for **mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation** in adults.[1]

Lucemyra is typically dosed four times daily during the period of peak withdrawal symptoms (generally the first 5 to 7 days following last use of opioid) with dosing guided by symptoms and adverse events.[1] Lucemyra treatment may continue for up to 14 days with dosing guided by symptoms. Discontinue Lucemyra with a gradual dose reduction over a 2- to 4-day period to mitigate Lucemyra withdrawal symptoms.

Disease Overview

Opioid use disorder is a primary, chronic and relapsing central nervous system (CNS) disease of brain reward, motivation, memory, and related circuitry characterized by an individual pathologically pursuing reward and/or relief by substance use and other behaviors.[2] Symptoms of opioid withdrawal usually begin two to three half-lives after the last opioid dose (6 to 12 hours for short half-life opioids such as heroin and morphine and 36 to 48 hours for long half-life opioids such as methadone).[3] Following cessation of a short half-life opioid, symptoms reach peak intensity within 2 to 4 days, with most of the physical withdrawal signs no longer apparent after 7 to 14 days. The duration of withdrawal also varies with the half-life of the opioid used and the duration of use. While opioid withdrawal is rarely life-threatening, the combination of uncomfortable symptoms and intense craving makes completion of withdrawal difficult for most people.

Guidelines

The American Society of Addiction Medicine (ASAM) practice guideline for the treatment of opioid use disorder (2020) discusses two primary strategies for the management of opioid withdrawal.[4] In one strategy, alpha-2 adrenergic agonists (i.e., clonidine, Lucemyra) are used along with other non-narcotic medications to reduce withdrawal symptoms such as nausea, vomiting, diarrhea, cramps, and sweating. The use of non-opioid medications may be the only option available in some healthcare settings and may also assist the transition of patients to opioid antagonist medications (i.e., naltrexone) helping to prevent subsequent relapse. Comparative data are limited but Lucemyra and clonidine appear to be similarly effective in the treatment of opioid withdrawal with hypotension occurring less frequently with Lucemyra. While clonidine is not FDA-approved for the treatment of opioid withdrawal, it has been extensively used off-label for this purpose. Clonidine can be combined with other non-narcotic medications targeting specific opioid withdrawal symptoms. ASAM states that alpha-2 adrenergic agonists are safe and effective for management of opioid withdrawal. However, the guideline notes that methadone and buprenorphine are more effective in reducing the symptoms of opioid withdrawal, in retaining patients in withdrawal management, and in supporting the completion of withdrawal management.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lucemyra. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lucemyra is recommended in those who meet the following criteria:

FDA-Approved Indication

51. Opioid Withdrawal Symptoms. Approve for 2 weeks (14 days) if the patient meets the following (A and B):
- **27.** Lucemyra is being used to facilitate abrupt opioid discontinuation; AND
- **28.** Patient has a of clonidine use (e.g., patches, tablets) and experienced unacceptable toxicity and/or inadequate efficacy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lucemyra is not recommended in the following situations:

61. Cannabis Use Disorder (Cannabis Dependence). One published study has evaluated the safety and efficacy of dronabinol and lofexidine in treating cannabis dependence (n = 156).[5] In this 11-week, placebo-controlled study, the combined intervention did not show efficacy as a treatment for cannabis use disorder.

62. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

63.

64.

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PRIOR AUTHORIZATION POLICY

POLICY: Lupus – Benlysta Intravenous Prior Authorization Policy
- Benlysta® (belimumab intravenous infusion – GlaxoSmithKline)

REVIEW DATE: 03/08/2023; selected revision 04/26/2023; 07/05/2023

OVERVIEW

Benlysta intravenous, a B-lymphocyte stimulator (BLyS)-specific inhibitor, is indicated for the following uses:[1]

- **Lupus nephritis**, in patients ≥ 5 years of age with active disease who are receiving standard therapy.
- **Systemic lupus erythematosus** (SLE), in patients ≥ 5 years of age with active, autoantibody-positive, systemic disease in those who are receiving standard therapy.

Benlysta intravenous has not been studied and is not recommended in those with severe active central nervous system lupus, or in combination with other biologics.

Guidelines

Benlysta is addressed in the following guidelines:

- **Lupus Nephritis:** Guidelines for lupus nephritis are available from the European League Against Rheumatism (EULAR) and European Renal Association/European Dialysis and Transplant Association (ERA-EDTA) [2019].[2] Benlysta may be considered as add-on treatment for non-responding/refractory lupus nephritis, to facilitate glucocorticoid sparing, control extra-renal lupus activity, and decrease the risk for extra-renal flares. Guidelines from Kidney Disease: Improving Global Outcomes (KDIGO) [2021] list Benlysta among the therapies recommended for second-line treatment of lupus nephritis.[3] The guidelines note that optimal use of Benlysta will become clearer as its use increases.
- **SLE:** Guidelines from the EULAR (2019) recommend consideration of add-on therapy with Benlysta for patients who have an inadequate response to standard of care (e.g., combinations of hydroxychloroquine and glucocorticoids with or without immunosuppressive agents).[4] EULAR defines an inadequate response as residual disease activity not allowing tapering of glucocorticoids and/or frequent relapses.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Benlysta intravenous. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Benlysta intravenous as well as the monitoring required for adverse events and long-term efficacy, approval requires Benlysta intravenous to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Benlysta intravenous is recommended in those who meet one of the following:

FDA-Approved Indications

E) Lupus Nephritis. Approve for the duration noted if the patient meets ONE of the following (A or B):
- **1.** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, and iv):
  - a. Patient is ≥ 5 years of age; AND
  - b. Diagnosis of lupus nephritis has been confirmed on biopsy; AND
    Note: For example, World Health Organization class III, IV, or V lupus nephritis.
  - c. The medication is being used concurrently with an immunosuppressive regimen; AND
    Note: Examples of an immunosuppressive regimen include azathioprine, cyclophosphamide, leflunomide, methotrexate, mycophenolate mofetil, and/or a systemic corticosteroid.
  - d. The medication is prescribed by or in consultation with a nephrologist or rheumatologist.
- **B)** Patient is Currently Receiving Benlysta Intravenous or Subcutaneous. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
  - **i.** The medication is being used concurrently with an immunosuppressive regimen; AND
    Note: Examples of an immunosuppressive regimen include azathioprine, cyclophosphamide, leflunomide, methotrexate, mycophenolate mofetil, and/or a systemic corticosteroid.
  - **ii.** The medication is prescribed by or in consultation with a nephrologist or rheumatologist.; AND
  - **iii.** Patient has responded to Benlysta subcutaneous or intravenous, as determined by the prescriber.
    Note: Examples of a response include improvement in organ dysfunction, reduction in flares, reduction in corticosteroid dose, decrease of anti-dsDNA titer, and improvement in complement levels (i.e., C3, C4).

1.

2. Systemic Lupus Erythematosus. Approve for the duration noted if the patient meets ONE of the following (A or B):
- **E)** Initial Therapy. Approve for 4 months if the patient meets ALL of the following (i, ii, iii, and iv):
  - **i.** Patient is ≥ 5 years of age; AND
  - **ii.** Patient has autoantibody-positive systemic lupus erythematosus (SLE), defined as positive for antinuclear antibodies (ANA) and/or anti-double-stranded DNA (anti-dsDNA) antibody; AND
    Note: Not all patients with SLE are positive for anti-dsDNA, but most will be positive for ANA.
  - **iii.** Patient meets ONE of the following (a or b):
    - **a)** The medication is being used concurrently with at least one other standard therapy; OR
      Note: Examples of standard therapies include an antimalarial (e.g., hydroxychloroquine), systemic corticosteroid (e.g., prednisone), and other immunosuppressants (e.g., azathioprine, mycophenolate mofetil, methotrexate).
    - **b)** Patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND
  - **iv.** The medication is prescribed by or in consultation with a rheumatologist, clinical immunologist, nephrologist, neurologist, or dermatologist.
- **B)** Patient is Currently Receiving Benlysta Intravenous or Subcutaneous. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
  - **i.** Patient meets ONE of the following (a or b):
    - **a)** The medication is being used concurrently with at least one other standard therapy; OR
      Note: Examples of standard therapies include an antimalarial (e.g., hydroxychloroquine), systemic corticosteroid (e.g., prednisone), and other immunosuppressants (e.g., azathioprine, mycophenolate mofetil, methotrexate).

b) Patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a rheumatologist, clinical immunologist, nephrologist, neurologist, or dermatologist; AND

iii. Patient has responded to Benlysta subcutaneous or intravenous, as determined by the prescriber.
Note: Examples of a response include reduction in flares, reduction in corticosteroid dose, decrease of anti-dsDNA titer, improvement in complement levels (i.e., C3, C4), or improvement in specific organ dysfunction (e.g., musculoskeletal, blood, hematologic, vascular, others).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Benlysta intravenous is not recommended in the following situations:

2. **Concurrent Use with Other Biologics.** Benlysta intravenous has not been studied and is not recommended in combination with other biologics.[1] Safety and efficacy have not been established with these combinations. See APPENDIX for examples of biologics that should not be taken in combination with Benlysta.

2. **Concurrent Use with Lupkynis (voclosporin capsules).** Lupkynis has not been studied in combination with biologics such as Benlysta.[1]

3. **Rheumatoid Arthritis.** A Phase II dose-ranging study evaluating patients with rheumatoid arthritis showed only small American College of Rheumatology (ACR) 20 responses with Benlysta (e.g., ACR 20 response at Week 24 was 28% with Benlysta 10 mg/kg).[5] Numerous other agents are available with higher ACR responses and established efficacy for RA.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Benlysta® injection [prescribing information]. Durham, NC: GlaxoSmithKline; February 2023.
2. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res (Hoboken).* 2012;64(6):797-808.
3. Rovin BH, Adler SG, Barratt J, et al. Executive summary of the KDIGO 2021 guideline for the management of glomerular diseases. *Kidney Int.* 2021;100(4):753-779.
4. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis.* 2019;78(6):736-745.
5. Stohl W, Merrill JT, McKay JD, et al. Efficacy and safety of belimumab in patients with rheumatoid arthritis: a phase II, randomized, double-blind, placebo-controlled, dose-ranging study. *J Rheumatol.* 2013;40(5):579-589.

APPENDIX

[*] Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; IV – Intravenous; BLyS – B-lymphocyte stimulator-specific inhibitor; SLE – Systemic lupus erythematosus; IFN – Interferon; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis.

PRIOR AUTHORIZATION POLICY

POLICY: Lupus – Benlysta Subcutaneous Prior Authorization Policy
- Benlysta® (belimumab subcutaneous injection – GlaxoSmithKline)

REVIEW DATE: 03/08/2023; selected revision 04/26/2023; 07/05/2023

OVERVIEW

Benlysta subcutaneous, a B-lymphocyte stimulator (BLyS)-specific inhibitor, is indicated for the following uses:[1]

- **Lupus nephritis**, in adults with active disease who are receiving standard therapy.
- **Systemic lupus erythematosus** (SLE), in patients ≥ 18 years of age with active, autoantibody-positive, systemic disease who are receiving standard therapy.

Benlysta subcutaneous has not been studied and is not recommended in those with severe, active central nervous system lupus, or in combination with other biologics.

Guidelines

Benlysta is addressed in the following guidelines:

- **Lupus Nephritis:** Guidelines for lupus nephritis are available from the European League Against Rheumatism (EULAR) and European Renal Association/European Dialysis and Transplant Association (ERA-EDTA) [2019].[2] Benlysta may be considered as add-on treatment for non-responding/refractory lupus nephritis, to facilitate glucocorticoid sparing, control extra-renal lupus activity, and decrease the risk for extra-renal flares. Guidelines from Kidney Disease: Improving Global Outcomes (KDIGO) [2021] list Benlysta among the therapies recommended for second-line treatment of lupus nephritis.[3] The guidelines note that optimal use of Benlysta will become clearer as its use increases.
- **SLE:** Guidelines from EULAR (2019) recommend consideration of add-on therapy with Benlysta for patients who have an inadequate response to standard of care (e.g., combinations of hydroxychloroquine and glucocorticoids with or without immunosuppressive agents).[4] EULAR defines an inadequate response as residual disease activity not allowing tapering of glucocorticoids and/or frequent relapses.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Benlysta subcutaneous. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Benlysta subcutaneous as well as the monitoring required for adverse events and long-term efficacy, approval requires Benlysta subcutaneous to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Benlysta subcutaneous is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Lupus Nephritis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Diagnosis of lupus nephritis has been confirmed on biopsy; AND
       Note: For example, World Health Organization class III, IV, or V lupus nephritis.
     - **iii.** The medication is being used concurrently with an immunosuppressive regimen; AND
       Note: Examples of an immunosuppressive regimen include azathioprine, cyclophosphamide, leflunomide, methotrexate, mycophenolate mofetil and/or a systemic corticosteroid.
     - **iv.** The medication is prescribed by or in consultation with a nephrologist or rheumatologist.
   - **B)** Patient is Currently Receiving Benlysta Subcutaneous or Intravenous. Approve for 1 year if the patient meets ALL of the following criteria (i, ii, and iii):
     - **i.** The medication is being used concurrently with an immunosuppressive regimen; AND
       Note: Examples of an immunosuppressive regimen include azathioprine, cyclophosphamide, leflunomide, methotrexate, mycophenolate mofetil and/or a systemic corticosteroid.
     - **ii.** The medication is prescribed by or in consultation with a nephrologist or rheumatologist; AND
     - **iii.** Patient has responded to Benlysta subcutaneous or intravenous, as determined by the prescriber.
       Note: Examples of a response include improvement in organ dysfunction, reduction in flares, reduction in corticosteroid dose, decrease of anti-dsDNA titer, and improvement in complement levels (i.e., C3, C4).

2. **Systemic Lupus Erythematosus (SLE).** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 4 months if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has autoantibody-positive SLE, defined as positive for antinuclear antibodies (ANA) and/or anti-double-stranded DNA (anti-dsDNA) antibody; AND
       Note: Not all patients with SLE are positive for anti-dsDNA, but most will be positive for ANA.
     - **iii.** Patient meets ONE of the following (a or b):
       - **a)** The medication is being used concurrently with at least one other standard therapy; OR
         Note: Examples of standard therapies include an antimalarial (e.g., hydroxychloroquine), systemic corticosteroid (e.g., prednisone), and other immunosuppressants (e.g., azathioprine, mycophenolate mofetil, methotrexate).
       - **b)** Patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND
     - **iv.** The medication is prescribed by or in consultation with a rheumatologist, clinical immunologist, nephrologist, neurologist, or dermatologist.
   - **B)** Patient is Currently Receiving Benlysta Subcutaneous or Intravenous. Approve for 1 year if the patient meets ALL of the following criteria (i, ii, and iii):
     - **i.** Patient meets ONE of the following (a or b):
       - **a)** The medication is being used concurrently with at least one other standard therapy; OR
         Note: Examples of standard therapies include an antimalarial (e.g., hydroxychloroquine), systemic corticosteroid (e.g., prednisone), and other immunosuppressants (e.g., azathioprine, mycophenolate mofetil, methotrexate).

b) Patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a rheumatologist, clinical immunologist, nephrologist, neurologist, or dermatologist; AND

iii. Patient has responded to Benlysta subcutaneous or intravenous, as determined by the prescriber.
Note: Examples of a response include reduction in flares, reduction in corticosteroid dose, decrease of anti-dsDNA titer, improvement in complement levels (i.e., C3, C4), or improvement in specific organ dysfunction (e.g., musculoskeletal, blood, hematologic, vascular, others).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Benlysta subcutaneous is not recommended in the following situations:

65. Concurrent Use with Other Biologics. Benlysta has not been studied and is not recommended in combination with other biologics.[1] Safety and efficacy have not been established with these combinations. See APPENDIX for examples of biologics that should not be taken in combination with Benlysta.

- **2. Concurrent Use with Lupkynis (voclosporin capsules).** Lupkynis has not been studied in combination with biologics such as Benlysta.[1]

3. Rheumatoid Arthritis. A Phase II dose-ranging study evaluating patients with rheumatoid arthritis showed only small American College of Rheumatology (ACR) 20 responses with Benlysta (e.g., ACR 20 response at Week 24 was 28% with Benlysta 10 mg/kg).[5] Numerous other agents are available with higher ACR responses and established efficacy for rheumatoid arthritis.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

6. Benlysta® injection [prescribing information]. Durham, NC: GlaxoSmithKline; February 2023.
7. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res (Hoboken)*. 2012;64(6):797-808.
8. Rovin BH, Adler SG, Barratt J, et al. Executive summary of the KDIGO 2021 guideline for the management of glomerular diseases. *Kidney Int*. 2021;100(4):753-779.
9. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis*. 2019;78(6):736-745.
10. Stohl W, Merrill JT, McKay JD, et al. Efficacy and safety of belimumab in patients with rheumatoid arthritis: a phase II, randomized, double-blind, placebo-controlled, dose-ranging Study. *J Rheumatol*. 2013;40(5):579-589.

APPENDIX

[*] Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; IV – Intravenous; BLyS – B-lymphocyte stimulator-specific inhibitor; SLE – Systemic lupus erythematosus; IFN – Interferon; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis.

PRIOR AUTHORIZATION POLICY

POLICY: Lupus – Lupkynis Prior Authorization Policy
- Lupkynis™ (voclosporin capsules – Aurinia)

REVIEW DATE: 03/08/2023; selected revision 07/05/2023

OVERVIEW

Lupkynis, a calcineurin inhibitor immunosuppressant, is indicated in combination with a background immunosuppressive therapy regimen for the treatment of active **lupus nephritis** in adults.[1]

Safety and efficacy have not been established in combination with cyclophosphamide, and this combination is not recommended. The recommended starting dose is 23.7 mg twice daily taken on an empty stomach, used in combination with mycophenolate mofetil and corticosteroids. Dose modifications are required based on estimated glomerular filtration rate (eGFR). Lupkynis is not recommended if baseline eGFR is ≤ 45 mL/min/1.73 m^2 unless the benefit exceeds the risk. If therapeutic benefit is not apparent by Week 24, consider discontinuation of Lupkynis.

Guidelines

Guidelines for lupus nephritis from the European League Against Rheumatism-European Renal Association-European Dialysis and Transplant Association (2019) recommend treatment based on disease classification.[2] Patient survival, long-term preservation of kidney function, and prevention of organ damage are among the goals of treatment. Patients with systemic lupus erythematosus with evidence of kidney involvement are recommended for kidney biopsy. First-line initial therapy for patients with Class III or IV disease (± Class V) includes mycophenolate mofetil or intravenous cyclophosphamide, in combination with glucocorticoids. In pure Class V disease, the first-line choice is mycophenolate mofetil + glucocorticoids. Following a response to initial therapy, mycophenolate mofetil or azathioprine (± low-dose glucocorticoids) are the drugs of choice for subsequent immunosuppressive treatment. Mycophenolate mofetil in combination with a calcineurin inhibitor (especially tacrolimus) is among the alternative therapies for those with nephrotic-range proteinuria or for Class V nephritis. Guidelines from Kidney Disease: Improving Global Outcomes (KDIGO)[2021] mention Lupkynis as a novel calcineurin inhibitor; however, a recommendation as to its place in therapy is not listed.[3] With approval of Lupkynis, multi-targeted therapy (e.g., glucocorticoid + mycophenolate mofetil + a calcineurin inhibitor) will be reassessed for a recommendation from KDIGO.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lupkynis. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lupkynis as well as the monitoring required for adverse events and long-term efficacy, approval requires Lupkynis to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lupkynis is recommended in those who meet the following criteria:

FDA-Approved Indication

3. Lupus Nephritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, and v):

- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Diagnosis of lupus nephritis has been confirmed on biopsy; AND
  Note: For example, World Health Organization class III, IV, or V lupus nephritis.
- **iii.** The medication is being used concurrently with an immunosuppressive regimen; AND
  Note: For example, mycophenolate mofetil or azathioprine with a systemic corticosteroid.
- **iv.** Patient has an estimated glomerular filtration rate (eGFR) > 45 mL/min/m^2; AND
- **v.** The medication is prescribed by or in consultation with a nephrologist or rheumatologist.

B) Patient is Currently Receiving Lupkynis. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, and iv):

- **i.** Patient is ≥ 18 years of age; AND
- **ii.** The medication is being used concurrently with an immunosuppressive regimen; AND
  Note: For example, mycophenolate mofetil or azathioprine with a systemic corticosteroid.
- **iii.** Patient has responded to Lupkynis, as determined by the prescriber; AND
  Note: Examples of a response include improvement in organ dysfunction, reduction in flares, reduction in corticosteroid dose, decrease of anti-double stranded DNA (anti-dsDNA) titer, and improvement in complement levels (i.e., C3, C4).
- **iv.** The medication is prescribed by or in consultation with a nephrologist or rheumatologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lupkynis is not recommended in the following situations:

66. Concurrent Use with Biologics or with Cyclophosphamide. Lupkynis has not been studied in combination with other biologics or cyclophosphamide.[1] Safety and efficacy have not been established with these combinations. See APPENDIX for examples of biologics that should not be taken in combination with Lupkynis.

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67. Plaque Psoriasis. In a Phase III trial, voclosporin was inferior to cyclosporine, which is an established therapy for plaque psoriasis.[4] Numerous other FDA-approved therapies are available with established efficacy for plaque psoriasis.

68. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

11. Lupkynis™ capsules [prescribing information]. Rockville, MD: Aurinia; January 2021.
12. Franouriakis A, Kostopoulou M, Cheema K, et al. 2019 Update of the Joint European League against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. *Ann Rheum Dis*. 2020;79(6):713-723.
13. Rovin BH, Adler SG, Barratt J, et al. Executive summary of the KDIGO 2021 guideline for the management of glomerular diseases. *Kidney Int*. 2021;100(4):753-779.
14. Li Y, Palmisano M, Sun D, Zhou Sl. Pharmacokinetic disposition difference between cyclosporine and voclosporin drives their distinct efficacy and safety profiles in clinical studies. *Clin Pharmacol*. 2020;12:83-96.

APPENDIX

[*] Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; IV – Intravenous; BLyS – B-lymphocyte stimulator-specific inhibitor; SLE – Systemic lupus erythematosus; IFN – Interferon; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis.

PRIOR AUTHORIZATION POLICY

POLICY: Lupus – Saphnelo Prior Authorization Policy
- Saphnelo® (anifrolumab-fnia intravenous infusion – AstraZeneca)

REVIEW DATE: 8/23/2023

OVERVIEW

Saphnelo, a type 1 interferon (IFN) receptor antagonist, is indicated for the treatment of moderate to severe **systemic lupus erythematosus (SLE)** in adults who are receiving standard therapy. Efficacy has not been evaluated and is not recommended in patients with severe active lupus nephritis or severe active central nervous system lupus.

Guidelines

Saphnelo is not addressed in current guidelines. European League Against Rheumatism guidelines for SLE (2019) recommend hydroxychloroquine for all patients, unless contraindicated.[2] Depending on the type and severity of organ involvement, glucocorticoids can be used but dosing should be minimized or withdrawn. Methotrexate, azathioprine, or mycophenolate should be considered in patients who do not respond to hydroxychloroquine ± glucocorticoids. Cyclophosphamide can be used for severe organ- or life-threatening disease or as rescue therapy in patients not responding to other immunosuppressive therapies. Add on treatment with Benlysta® (belimumab intravenous infusion or subcutaneous injection) should be considered for those who do not respond to standard of care with hydroxychloroquine + glucocorticoids ± immunosuppressive therapies. Rituximab can also be considered for organ-threatening disease or for those with intolerance or contraindications to standard immunosuppressives.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Saphnelo. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Saphnelo as well as the monitoring required for adverse events and long-term efficacy, approval requires Saphnelo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Saphnelo is recommended in those who meet the following criteria:

FDA-Approved Indication

3. Systemic Lupus Erythematosus. Approve for the duration noted if the patient meets ONE of the following (A or B):

F) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, and iv):

iv. Patient is ≥ 18 years of age; AND

v. Patient has autoantibody-positive SLE, defined as positive for at least one of the following: antinuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA) antibodies, anti-Smith (anti-Sm) antibodies; AND
Note: Not all patients with SLE are positive for anti-dsDNA, but most will be positive for ANA.

vi. Patient meets ONE of the following (a or b):
- **a)** The medication is being used concurrently with at least one other standard therapy; OR
  Note: Examples of standard therapies include an antimalarial (e.g., hydroxychloroquine), systemic corticosteroid (e.g., prednisone), and other immunosuppressants (e.g., azathioprine, mycophenolate mofetil, methotrexate).
- **b)** Patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND

vii. The medication is prescribed by or in consultation with a rheumatologist, clinical immunologist, nephrologist, neurologist, or dermatologist.

C) Patient is Currently Receiving Saphnelo. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient meets ONE of the following (a or b):
- **a)** The medication is being used concurrently with at least one other standard therapy; OR
  Note: Examples of standard therapies include an antimalarial (e.g., hydroxychloroquine), systemic corticosteroid (e.g., prednisone), and other immunosuppressants (e.g., azathioprine, mycophenolate mofetil, methotrexate).
- **b)** Patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND

ii. Patient responded to Saphnelo, as determined by the prescriber; AND
Note: Examples of a response include reduction in flares, reduction in corticosteroid dose, decrease of anti-dsDNA titer, improvement in complement levels (i.e., C3, C4), or improvement in specific organ dysfunction (e.g., musculoskeletal, blood, hematologic, vascular, others).

iii. The medication is prescribed by or in consultation with a rheumatologist, clinical immunologist, nephrologist, neurologist, or dermatologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Saphnelo is not recommended in the following situations:

1. **Concurrent Use with Other Biologics.** Saphnelo has not been studied and is not recommended in combination with other biologics (e.g., Benlysta [belimumab intravenous infusion or subcutaneous injection], rituximab).[1] Safety and efficacy have not been established with these combinations. See APPENDIX for examples of other biologics that should not be taken in combination with Saphnelo.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

15. Saphnelo® injection, for intravenous use [prescribing information]. Wilmington DE: AstraZeneca; September 2022.
16. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis*. 2019;78(6):736-745.

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* Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; IFN – Interferon; SLE – Systemic lupus erythematosus; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis.

PRIOR AUTHORIZATION POLICY

POLICY: Makena (hydroxyprogesterone caproate) Prior Authorization Policy
- Makena® (hydroxyprogesterone caproate injection [subcutaneous and intramuscular] – AMAG/Covis, generics [intramuscular only]); discontinued

REVIEW DATE: 11/15/2023; Policy will be retired 01/01/2024

OVERVIEW

Makena was an injectable progestin which was indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.[1] The effectiveness of Makena was based on improvement in the proportion of women who delivered < 37 weeks of gestation. On April 6, 2023, Makena and its generics were withdrawn from the market. The FDA recognized that a limited supply of the product had already been distributed and advised patients to consult with their healthcare provider.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Makena (hydroxyprogesterone caproate). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of hydroxyprogesterone caproate (Makena, generics) is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Reduce Risk of Preterm Birth.** Approve for up to 5 months of therapy (21 injections) in patients who meet the following criteria (A, B, and C):
   - **A)** Patient is currently receiving hydroxyprogesterone caproate (Makena or generics); AND
   - **B)** Patient is pregnant with a singleton pregnancy; AND
   - **C)** Patient has a history of singleton spontaneous preterm birth prior to 37 weeks gestation.

   Note: In cases where there was an inaccuracy in dating the pregnancy, a one-month authorization may be granted to patients who have already received 21 injections and are < 37 weeks pregnant.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Makena (hydroxyprogesterone caproate (Makena, generics) is not recommended in the following situations:

1. **History of a Threatened Preterm Birth.** Makena is not indicated in pregnant women who experienced a past threatened preterm birth but delivered a full-term infant after 36 completed weeks of gestation.[1]

2. **Infertility.** Some studies have evaluated hydroxyprogesterone caproate as the progesterone used in *in vitro* fertilization.[5,6] However, progesterone in oil or vaginally administered progesterone are mentioned for use during the luteal phase and in early pregnancy in the treatment of infertility by an educational bulletin by the Practice Committee of the American Society of Reproductive Medicine.[7]

3. **Patients Pregnant with Multiple Gestations.** Makena is not indicated in patients pregnant with multiple gestations (e.g., twins, triplets, or other multiples).[1]

4. **Pregnant Patient with Short Cervix Without a History of a Prior Singleton Spontaneous Preterm Birth.** Makena is not indicated for use in pregnant women with short cervix and no of singleton spontaneous pre-term birth prior to 37 weeks gestation.[1]

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

322. Makena® for intramuscular or subcutaneous use [prescribing information]. Waltham, MA: AMAG; December 2022.
323. FDA commissioner and chief scientist announce decision to withdraw approval of Makena [press release]. April 6, 2023. Available at: FDA Commissioner and Chief Scientist Announce Decision to Withdraw Approval of Makena | FDA. Accessed on April 6, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Betaine Anhydrous Prior Authorization Policy
- Cystadane® (betaine anhydrous powder – Recordati Rare Diseases, generic)

REVIEW DATE: 08/30/2023

OVERVIEW

Betaine anhydrous powder (Cystadane, generic), a methylating agent, is indicated for the treatment of **homocystinuria** to decrease elevated homocysteine blood concentrations in adults and pediatric patients.[1] Included within the category of homocystinuria are cystathionine beta-synthase deficiency, 5,10-methylenetetrahydrofolate reductase deficiency, and cobalamin cofactor metabolism defect.

Disease Overview

Homocystinuria is a group of rare, autosomal recessive disorders caused by mutations in specific enzymes that metabolize amino acids.[2,3] Elevated levels of homocysteine can lead to abnormalities in the central nervous system, eye, skeletal system, and vascular system.

Clinical Efficacy

Clinical and observational studies demonstrated patients with homocystinuria who received betaine anhydrous powder had significant reductions plasma homocystine or homocysteine concentrations.[1] Additionally, improvement in seizures or behavioral and cognitive functioning were reported for many patients. Many of these patients were also taking other therapies such as vitamin B6 (pyridoxine), vitamin B12 (cobalamin), and folate with variable biochemical responses.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of betaine anhydrous powder (Cystadane, generic). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with betaine anhydrous powder (Cystadane, generic) as well as the monitoring required for adverse events and long-term efficacy, approval requires betaine anhydrous powder (Cystadane, generic) to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of betaine anhydrous powder (Cystadane, generic) is recommended in those who meet the following criteria:

FDA-Approved Indication

142. Homocystinuria. Approve for 1 year if the patient meets the following (A, B, and C):

A) Patient has a confirmed diagnosis based on genetic testing demonstrating one of the following (i, ii, or iii):
- **i.** Cystathionine beta-synthase deficiency; OR
- **ii.** 5,10-methylenetetrahydrofolate reductase deficiency; OR

iii. Cobalamin cofactor metabolism defect; AND

B) Patient has tried or is concurrently receiving vitamin B6 (pyridoxine), vitamin B12 (cobalamin), or folate supplementation; AND

C) The medication is prescribed by or in consultation with a geneticist, metabolic disease specialist, or a physician who specializes in the management of homocystinuria.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of betaine anhydrous powder (Cystadane, generic) is not recommended in the following situations:

203. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

648. Cystadane® powder [prescribing information]. Lebanon, NJ: Recordati Rare Diseases; October 2019.
649. Truitt C, Hoff WD, Deole R. Health functionalities of betaine in patients with homocystinuria. *Front Nutr*. 2021 Sep 9;8:690359.
650. Morris A, Kožich V, Santra S, et al. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. *J Inherit Metab Dis*. 2017 Jan;40(1):49-74.

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Carbaglu Prior Authorization Policy
- Carbaglu® (carglumic acid tablets for oral suspension – Recordati Rare Diseases)

REVIEW DATE: 01/18/2023

OVERVIEW

Carbaglu, a carbamoyl phosphate synthetase 1 (CPS 1) activator, is indicated as adjunct therapy to standard of care for the following uses:[1]

- **N-acteylglutamate synthase (NAGS) deficiency** with acute or chronic hyperammonemia.
- **Propionic acidemia or methylmalonic acidemia** with acute hyperammonemia.

For NAGS deficiency, the prescribing information notes that treatment with Carbaglu should be initiated as soon as the disorder is suspected, which may be as soon as birth.[1]

For acute hyperammonemia due to propionic acidemia or methylmalonic acidemia, Carbaglu is indicated as adjunctive therapy for acute treatment.[1] In this setting, Carbaglu should be continued until the patient's ammonia level is < 50 micromol/L and for a maximum duration of 7 days.

Disease Overview

NAGS Deficiency

Carbaglu is a synthetic analog of N-acetylglutamate, which activates CPS 1, the first reaction in the urea cycle.[1] The function of the urea cycle is to convert ammonia into urea for urinary excretion. In the case of NAGS deficiency, N-acetylglutamate is not sufficiently produced due to lack of the NAGS enzyme.[2] NAGS deficiency is the rarest urea cycle disorder with an estimated incidence of less than 1:2,000,000 live births. Age of diagnosis can vary from neonatal to adulthood; based on literature review, most cases present in the early neonatal period. Therefore, newborn screening is of limited value as patients are likely to be symptomatic before screening results are available. Common presenting features include poor feeding, vomiting, lethargy, decreased consciousness, seizures, and hypotonia. Laboratory abnormalities include hyperammonemia which can lead to significant morbidity and mortality in severe cases. Genetic testing is required to confirm the diagnosis; however, given the delays involved with genetic testing, it has been suggested that a therapeutic trial of Carbaglu should be initiated for any patient with unexplained hyperammonemia.

Propionic Acidemia and Methylmalonic Acidemia

In propionic and methylmalonic acidemias, other enzymatic defects result in accumulation of propionyl-coenzyme A (CoA), which acts as a competitive inhibitor for NAGS.[3,4] The incidence of propionic acidemia is 1:100,000 to 1:150,000, and the incidence of methylmalonic acidemia is 1:50,000.[3] According to guidelines for management of propionic acidemia and methylmalonic acidemia (2021), these disorders should be considered in any newborn/child (critically ill or not) with unexplained metabolic acidosis (with elevated anion gap); elevated lactate; hyperammonemia; leukopenia, thrombocytopenia, anemia; and/or urine ketone bodies. If ammonia is increased, further metabolic investigations should be performed immediately but specific treatment must not be delayed. Carbaglu is supported as part of the initial management plan for symptomatic hyperammonemia both in patients with known propionic/methylmalonic acidemia and in undiagnosed patients. Other elements of initial management include cessation of protein intake, use of intravenous glucose and insulin, and other medications such as carnitine and vitamin B_{12}.

Extracorporeal detoxification (i.e., dialysis) may be used in some cases, particularly for extremely elevated ammonia levels.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Carbaglu. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Carbaglu as well as the monitoring required for adverse events and long-term efficacy, approval requires Carbaglu to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Carbaglu is recommended in those who meet one of the following criteria:

FDA-Approved Indications

143. N-Acetylglutamate Synthase Deficiency with Hyperammonemia. Approve for the duration noted below if the patient meets the following criteria (A, B, and C):

- **A)** According to the prescriber, diagnosis is supported by one of the following (i or ii):
  - **i.** Approve for 1 year if genetic testing confirmed a mutation leading to N-acetylglutamate synthase deficiency; OR
  - **ii.** Approve for 3 months if the patient has hyperammonemia diagnosed with an ammonia level above the upper limit of the normal reference range for the reporting laboratory.
    Note: Reference ranges are dependent upon patient's age; AND
- **B)** The medication is prescribed in conjunction with a protein-restricted diet; AND
- **C)** The medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).

144. Propionic Acidemia or Methylmalonic Acidemia with Hyperammonemia, Acute Treatment. Approve for 7 days if the patient meets the following criteria (A, B, and C):

- **A)** Patient's plasma ammonia level is ≥ 50 micromol/L; AND
- **B)** The medication is prescribed in conjunction with other ammonia-lowering therapies; AND
  Note: Examples of other ammonia-lowering therapies include intravenous glucose, insulin, L-carnitine, protein restriction, and dialysis.
- **C)** The medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Carbaglu is not recommended in the following situations:

204. Propionic Acidemia or Methylmalonic Acidemia with Hyperammonemia, Maintenance. Chronic use of Carbaglu (beyond 7 days) for propionic acidemia or methylmalonic acidemia is not indicated.[1] There is no clinical evidence for long-term use of Carbaglu in propionic acidemia or methylmalonic acidemia.[3]

205. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

651. Carbaglu® tablets [prescribing information]. Lebanon, NJ: Recordati Rare Diseases; August 2021.
652. Kenneson A, Singh RH. Presentation and management of N-acetylglutamate synthase deficiency: a review of the literature. *Orphanet J Rare Dis*. 2020;15(1):279.
653. Forny P, Hörster F, Ballhausen D, et al. Guidelines for the diagnosis and management of methylmalonic acidaemia and propionic acidaemia: First revision. *J Inherit Metab Dis*. 2021 May;44(3):566-592.
654. Haijes HA, van Hasselt PM, Jans JJM, Verhoeven-Duif NM. Pathophysiology of propionic and methylmalonic acidemias. Part 2: Treatment strategies. *J Inherit Metab Dis*. 2019 Sep;42(5):745-761.

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Dojolvi Prior Authorization Policy
- Dojolvi™ (triheptanoin oral liquid – Ultragenyx)

REVIEW DATE: 07/26/2023

OVERVIEW

Dojolvi, a synthetic medium odd-chain triglyceride, is indicated as a source of calories and fatty acids for the treatment of adults and pediatric patients with molecularly confirmed **long-chain fatty acid oxidation disorders (LC-FAODs)**.[1]

For a patient receiving another medium-chain triglyceride product, discontinue prior to the first dose of Dojolvi.

Disease Overview

LC-FAODs are a group of autosomal recessive genetic metabolic disorders in which the body is unable to properly oxidize long-chain fatty acid in the mitochondria (normally an important energy pathway when glucose is low).[2,3] The four most commonly affected enzymes are carnitine palmitoyl transferase 2 (CPT-2), very long-chain acyl-CoA dehydrogenase (VLCAD), long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), and mitochondrial trifunctional protein (TFP).[4] Other less common mutations may also occur.[2,4] Onset may occur anywhere from the neonatal period to adulthood. Clinical manifestations are heterogeneous and not well correlated with genotype.[2] Diagnosis of LC-FAODs has increased with the use of routine newborn screening. Newborn screening tests measure acylcarnitines in dried blood spots.[5] Abnormal newborn screening results or the presence of symptoms associated with LC-FAODs warrant further evaluation involving plasma acylcarnitine measurement, enzyme activity assays, and/or genetic testing. The activity of specific enzymes can be measured in lymphocytes or skin fibroblasts since these cells express all enzymes involved in long-chain fatty acid oxidation.[3] Mutation analysis can identify the specific genetic defect. However, new mutations and variants are regularly identified, requiring functional studies such as enzyme activity measurements for confirmation of the diagnosis.

Guidelines

A consensus statement regarding treatment recommendations in LC-FAODs was published in 2009; Dojolvi is not specifically addressed, although medium-chain triglycerides are discussed more broadly.[6] In general, it is noted that the clinical course of LC-FAODs is unpredictable, and medium-chain triglyceride supplementation is an important part of the management strategy for many patients.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Dojolvi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Dojolvi as well as the monitoring required for adverse events and long-term efficacy, approval requires Dojolvi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Dojolvi is recommended in those who meet the following criteria:

FDA-Approved Indication

145. Long-Chain Fatty Acid Oxidation Disorders. Approve for 1 year if the patient meets the following (A, B, C, and D):

A) Patient has a molecularly confirmed diagnosis of a long-chain fatty acid oxidation disorder based on at least TWO of the following (TWO of i, ii, or iii):

i. Disease-specific elevations of acylcarnitines on a newborn blood spot or in plasma; OR

ii. Enzyme activity assay (in cultured fibroblasts or lymphocytes) below the lower limit of the normal reference range for the reporting laboratory; OR

Note: Examples of enzyme assays include carnitine palmitoyl transferase 2 (CPT-2), very long-chain acyl-CoA dehydrogenase (VLCAD), long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), and mitochondrial trifunctional protein (TFP).

iii. Genetic testing demonstrating pathogenic mutation in a gene associated with long-chain fatty acid oxidation disorders; AND

Note: Examples of genes associated with long-chain fatty acid disorders include *CPT2* (encodes CPT-2), *ACADVL* (encodes VLCAD), *HADHA* (encodes LCHAD and TFP), and *HADHB* (encodes TFP).

B) Patient will not use any other medium-chain triglyceride products concomitantly with Dojolvi; AND

C) Patient meets at least one of the following (i, ii, or iii):

i. According to the prescriber, the patient has had inadequate efficacy or significant intolerance to an over-the-counter medium-chain triglyceride product (e.g. nutraceutical supplements) [other than Dojolvi]; OR

ii. According to the prescriber, the patient has a of at least one severe or recurrent manifestation of long-chain fatty acid oxidation disorders (i.e., cardiomyopathy, rhabdomyolysis, or hypoglycemia); OR

iii. Patient is currently receiving Dojolvi; AND

D) The medication is prescribed by or in consultation with a metabolic disease specialist or a physician who specializes in the management of long-chain fatty acid oxidation disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Dojolvi is not recommended in the following situations:

206. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

655. Dojolvi™ oral liquid [prescribing information]. Novato, CA: Ultragenyx; November 2021.
656. Merritt JL II, Norris M, Kanungo S. Fatty acid oxidation disorders. *Ann Transl Med*. 2018;6(24):473.
657. Knotterus SJG, Bleeker JC, Wüst RCI, et al. Disorders of mitochondrial long-chain fatty acid oxidation and the carnitine shuffle. *Rev Endocr Metab Disord*. 2018;19:93-106.
658. Vockley J, Burton B, Berry GT, et al. UX007 for the treatment of long chain-fatty acid oxidation disorders: safety and efficacy in children and adults following 24 weeks of treatment. *Mol Genet Metab*. 2017;120(4):370-77.
659. ACT Sheets and Algorithms: Newborn Screening ACT Sheets and Algorithms. American College of Molecular Genetics and Genomics. Available at: https://www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx. Accessed on July 18, 2023.
660. Spiekerkoetter U, Lindner M, Santer R, et al. Treatment recommendations in long-chain fatty acid oxidation defects: consensus from a workshop. *J Inherit Metab Dis*. 2009;32(4):498-505.

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Imcivree Prior Authorization Policy
- Imcivree® (setmelanotide subcutaneous injection – Rhythm)

REVIEW DATE: 01/04/2023

OVERVIEW

Imcivree, a melanocortin 4 receptor agonist, is indicated for chronic weight management in patients ≥ 6 years of age with monogenic or syndromic obesity due to:[1]

- **Proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency**, as determined by an FDA-approved test demonstrating variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance.
- **Bardet-Biedl Syndrome**.

As a limitation of use, Imcivree is not indicated for obesity due to suspected POMC, PCSK1, or LEPR deficiency with *POMC*, *PCSK1*, or *LEPR* variants classified as benign or likely benign.[1] Imcivree is also not indicated for obesity not related to POMC, PCSK1, or LEPR deficiency or not related to Bardet-Biedl syndrome, including obesity associated with other genetic syndromes and general (polygenic) obesity.

In the pivotal trial for Imcivree obesity due to POMC deficiency (homozygous or compound heterozygous variants in *POMC* or *PCSK1*) or LEPR deficiency (homozygous or compound heterozygous variants in *LEPR*), obesity was defined according to patient age.[2] For patients 6 to < 18 years of age, obesity was defined as body weight ≥ 95th percentile for age on growth chart assessment. For patients ≥ 18 years of age, obesity was defined as a body mass index (BMI) ≥ 30 kg/m^2.

Per the Imcivree prescribing information, select patients for treatment with Imcivree who have a clinical diagnosis of Bardet-Biedl syndrome.[1] It is noted that in the pivotal trial, adults had a BMI ≥ 30 kg/m^2 and pediatric patients had a weight ≥ 97th percentile using growth chart assessments. Patients were enrolled who had a clinical diagnosis of Bardet-Biedl syndrome. The clinical diagnosis was based on Beales criteria, which require that four primary features, or three primary and two secondary features, of Bardet-Biedl syndrome be met.[3]

For obesity due to POMC, PCSK1, or LEPR deficiency, weight loss should be evaluated after 12 to 16 weeks of Imcivree treatment.[1] If a patient has not lost at least 5% of baseline body weight, or 5% of baseline body mass index for a patient with continued growth potential, Imcivree should be discontinued as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment. For obesity and a clinical diagnosis of Bardet-Biedl syndrome, evaluate weight loss after 1 year of treatment. If a patient has not lost at least 5% of baseline body weight, or 5% of baseline BMI for a patient < 18 years of age, discontinue Imcivree.

Disease Overview

Monogenic obesity is a rare and severe early-onset form of obesity.[4] Unlike general obesity, environmental factors are much less impactful on obesity development in these patients. Fewer than 50 patients worldwide have been identified with POMC deficiency (*POMC* or *PCSK1* mutations); the prevalence of LEPR deficiency is unknown but is expected to account for less than 3% of severe early-onset obesity. The true prevalence of these disorders is unknown and likely underestimated due to lack of provider awareness and

genetic testing.[2] Clinical presentation is mainly characterized by major hyperphagia and ravenous hunger.[3] Patients with these disorders experience very rapid and early increase in weight, occurring within the first few days of life to early childhood. Lifestyle interventions may provide initial weight loss but are very difficult to maintain long-term in this population due to constant, insatiable hunger.[5] Isolated case reports of bariatric surgery have demonstrated some efficacy but are generally regarded as disappointing relative to the general population, likely related to the underlying energy imbalance. Caution is urged before considering bariatric surgery in patients with monogenic obesity disorders.

Bardet-Biedl syndrome is a rare genetic disease of obesity with an estimated prevalence of 1:100,000 individuals in Northern Europe and America, although the prevalence can be higher in certain consanguineous populations.[6] It is generally inherited in an autosomal recessive fashion. There are many gene mutations which are known to lead to the development of Bardet-Biedl syndrome. Additionally, an estimated 20% to 30% of patients with Bardet-Biedl syndrome do not have an identified genetic mutation. Diagnosis is based on the presence of characteristic clinical findings.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Imcivree. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Imcivree as well as the monitoring required for adverse events and long-term efficacy, approval requires Imcivree to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Imcivree is recommended in those who meet one of the following criteria:

FDA-Approved Indications

146. Obesity Due to Proopiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency. Approve for the duration noted if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets the following criteria (i, ii, iii, and iv):

- **i.** Patient is ≥ 6 years of age; AND
- **ii.** Patient meets both of the following criteria (a and b):
  - **a)** Genetic testing demonstrates homozygous or compound heterozygous mutations in one of the following genes: *POMC, PCSK1*, or *LEPR*; AND
  - **b)** The genetic variant is interpreted as pathogenic, likely pathogenic, or of uncertain significance; AND
- **iii.** Patient meets one of the following criteria (a or b):
  - **a)** Patient is ≥ 18 years of age: Patient currently has a body mass index (BMI) ≥ 30 kg/m^2; OR
  - **b)** Patient is 6 to 17 years of age: Patient currently has a body weight ≥ 95th percentile for age on growth chart assessment; AND
- **iv.** Imcivree is prescribed by or in consultation with an endocrinologist, a geneticist, or a physician who specializes in metabolic disorders.

B) Patient is currently receiving Imcivree. Approve for 1 year if the patient meets the following criteria (i, ii, iii, and iv):
Note: For a patient who has not completed at least 4 months of Imcivree therapy, refer to Initial Therapy criteria.
- **i.** Patient is ≥ 6 years of age; AND
- **ii.** Patient meets both of the following criteria (a and b):
  - **a)** Genetic testing demonstrates homozygous or compound heterozygous mutations in one of the following genes: *POMC*, *PCSK1*, or *LEPR*; AND
  - **b)** The genetic variant is interpreted as pathogenic, likely pathogenic, or of uncertain significance; AND
- **iii.** Patient meets one of the following criteria (a or b):
  - **a)** Patient has lost ≥ 5% of baseline body weight since initiating Imcivree therapy; OR
  - **b)** Patient meets both of the following [(1) and (2)]:
    - **(1)** Patient has continued growth potential; AND
    - **(2)** Patient has lost ≥ 5% of baseline BMI since initiating Imcivree therapy; AND
- **iv.** Imcivree is prescribed by or in consultation with an endocrinologist, a geneticist, or a physician who specializes in metabolic disorders.

147. Obesity Due to Bardet-Biedl Syndrome. Approve for 1 year if the patient meets one of the following (A or B):

A) Initial Therapy. Approve if the patient meets all of the following criteria (i, ii, iii, and iv):
- **i.** Patient is ≥ 6 years of age; AND
- **ii.** Patient has a clinical diagnosis of Bardet-Biedl Syndrome by meeting one of the following (a or b):
  - **a)** Patient has at least FOUR of the following primary features of Bardet-Biedl Syndrome: rod-cone dystrophy, polydactyly, obesity, learning disability, renal anomalies, or male hypogonadism; OR
  - **b)** Patient meets both of the following [(1) and (2)]:
    - **(1)** Patient has at least THREE of the following primary features of Bardet-Biedl Syndrome: rod-cone dystrophy, polydactyly, obesity, learning disability, renal anomalies, or male hypogonadism; AND
    - **(2)** Patient has at least TWO of the following secondary features of Bardet-Biedl Syndrome: speech disorder/delay, strabismus/cataracts/astigmatism, brachydactyly/syndactyly, developmental delay, polyuria/polydipsia (nephrogenic diabetes insipidus), ataxia/poor coordination/imbalance, mild spasticity, diabetes mellitus, dental crowding/hypodontia/small roots/high arched palate, left ventricular hypertrophy/congenital heart disease, or hepatic fibrosis; AND
- **iii.** Patient meets one of the following criteria (a or b):
  - **a)** Patient is ≥ 18 years of age: Patient currently has a body mass index (BMI) ≥ 30 kg/m^2; OR
  - **b)** Patient is < 18 years of age: Patient currently has a body weight ≥ 97th percentile for age on growth chart assessment; AND
- **iv.** Imcivree is prescribed by or in consultation with an endocrinologist, a geneticist, or a physician who specializes in metabolic disorders.

B) Patient is Currently Receiving Imcivree. Approve if the patient meets the following criteria (i, ii, and iii):
Note: For a patient who has not completed at least 1 year of Imcivree therapy, refer to Initial Therapy criteria.
- **i.** Patient is ≥ 6 years of age; AND
- **ii.** Patient meets one of the following criteria (a or b):

a) Patient has lost ≥ 5% of baseline body weight since initiating Imcivree therapy; OR
b) Patient meets both of the following [(1) and (2)]:
(1) Patient is < 18 years of age; AND
(2) Patient has lost ≥ 5% of baseline BMI since initiating Imcivree therapy; AND

iii. Imcivree is prescribed by or in consultation with an endocrinologist, a geneticist, or a physician who specializes in metabolic disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Imcivree is not recommended in the following situations:

207. Other Genetic Obesity Syndromes. Imcivree is not indicated for genetic obesity syndromes other than POMC-, PCSK1-, or LEPR-deficient obesity or Bardet-Biedl syndrome.
Note: Examples of genetic obesity syndromes include Prader-Willi syndrome and Alström syndrome.

208. General Obesity. Imcivree is not indicated in this setting and there are no clinical data to support its use.[1]

209. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

324. Imcivree® subcutaneous injection [prescribing information]. Boston, MA: Rhythm; June 2022.
325. Clément K, van den Akker E, Argente J, et al; setmelanotide POMC and LEPR Phase 3 Trial Investigators. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. *Lancet Diabetes Endocrinol*. 2020 Dec;8(12):960-970.
326. Haws RM, Gordon G, Han JC, et al. The efficacy and safety of setmelanotide in individuals with Bardet-Biedl syndrome or Alström syndrome: Phase 3 trial design. *Contemp Clin Trials Commun*. 2021 May 3;22:100780.
327. Huvenne H, Dubern B, Clément K, Poitou C. Rare genetic forms of obesity: clinical approach and current treatments in 2016. *Obes Facts*. 2016;9(3):158-73.
328. Poitou C, Mosbah H, Clément K. Mechanisms in endocrinology: update on treatments for patients with genetic obesity. *Eur J Endocrinol*. 2020 Nov;183(5):R149-R166.
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PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Nitisinone Products Prior Authorization Policy
- Orfadin® (nitisinone capsules and suspension – Sobi, generic [capsules only])
- Nityr® (nitisinone tablets – Cycle)

REVIEW DATE: 11/15/2023

OVERVIEW

Nitisinone products are hydroxy-phenylpyruvate dioxygenase inhibitors indicated for the treatment of **hereditary tyrosinemia type 1** in combination with dietary restriction of tyrosine and phenylalanine in pediatric patients and adults.[1,2]

Disease Overview

Hereditary tyrosinemia type 1 is a genetic disorder characterized by elevated blood levels of the amino acid tyrosine.[3,4] It is caused by mutations in the *FAH* gene, which lead to a deficiency of the enzyme fumarylacetoacetate hydrolase that is required for the breakdown of tyrosine. Symptoms usually appear in the first few months after birth and include failure to thrive, diarrhea, vomiting, jaundice, cabbage-like odor, and increased tendency to bleed. Diagnosis is most often via newborn screening (i.e., elevated alpha-fetoprotein and succinylacetone); however, carrier genetic testing and prenatal diagnosis by detection of succinylacetone in the amniotic fluid are also possible. Treatment should be initiated immediately upon diagnosis with a diet restricted in tyrosine and phenylalanine and with nitisinone, which blocks the second step in the tyrosine degradation pathway.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of nitisinone products. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with nitisinone products as well as the monitoring required for adverse events and long-term efficacy, approval requires the agent to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of nitisinone products is recommended in those who meet the following criteria:

FDA-Approved Indication

148. Hereditary Tyrosinemia Type 1. Approve for 1 year if the patient meets the following (A, B, C, and D):
- **A)** According to the prescriber, diagnosis is supported by one of the following (i or ii):
  - **i.** Genetic testing confirms biallelic pathogenic/likely pathogenic variants in the FAH gene; OR
  - **ii.** Patient has elevated levels of succinylacetone in the serum or urine; AND
- **B)** The medication is prescribed in conjunction with a tyrosine- and phenylalanine-restricted diet; AND
- **C)** Patient will not be taking the requested agent concurrently with another nitisinone product; AND

Note: Examples of nitisinone products include Orfadin, generic nitisinone capsules, and Nityr. Concurrent use of these agents is not allowed.

D) The medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of nitisinone products is not recommended in the following situations:

210. Concomitant Therapy with Nitisinone Products. Note: For example, concomitant use of Orfadin, generic nitisinone capsules, and/or Nityr. There are no data available to support concomitant use.

211. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

661. Orfadin® capsules and suspension [prescribing information]. Waltham, MA: Sobi; November 2021.
662. Nityr® tablets [prescribing information]. Cambridge, UK: Cycle; June 2021.
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664. Tyrosinemia type 1. National Organization for Rare Disorders. Updated September 2019. Available at: https://rarediseases.org/rare-diseases/tyrosinemia-type-1/. Accessed on November 9, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Nulibry Prior Authorization Policy
- Nulibry™ (fosdenopterin intravenous infusion – Origin Biosciences)

REVIEW DATE: 03/29/2023

OVERVIEW

Nulibry, a cyclic pyranopterin monophosphate (cPMP), is indicated to reduce the risk of mortality in patients with **molybdenum cofactor deficiency** (MoCD) **Type A**.[1]

MoCD is a rare, life-threatening, autosomal-recessive disorder characterized by the deficiency of three molybdenum-dependent enzymes: sulfite oxidase (SOX), xanthine dehydrogenase, and aldehyde oxidase.[2] Patients with MoCD Type A have mutations in the *MOCS1* gene leading to deficiency of the intermediate substrate, cPMP.[1] Substrate replacement therapy with Nulibry provides an exogenous source of cPMP, which is converted to molybdopterin. Molybdopterin is then converted to molybdenum cofactor, which is needed for the activation of molybdenum-dependent enzymes, including SOX, an enzyme that reduces levels of neurotoxic sulfites.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Nulibry. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nulibry as well as the monitoring required for adverse events and long-term efficacy, approval requires Nulibry to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nulibry is recommended in those who meet the following criteria:

FDA-Approved Indication

149. Molybdenum Cofactor Deficiency (MoCD) Type A. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **A)** Patient has genetic testing confirmation of a mutation in the *MOCS1* gene; AND
- **B)** According to the prescriber, based on the current condition, the patient is expected to derive benefit with Nulibry and the disease state is NOT considered to be too advanced; AND
- **C)** The medication is prescribed by or in consultation with a pediatrician, geneticist, or a physician who specializes in molybdenum cofactor deficiency (MoCD) Type A.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nulibry is not recommended in the following situations:

212. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

665. Nulibry intravenous infusion [prescribing information]. Boston, MA: Origin Biosciences; October 2022.
666. Mechler K, Mountford WK, Hoffmann GF, et al. Ultra-orphan diseases: a quantitative analysis of the natural of molybdenum cofactor deficiency. *Genet Med*. 2015 Dec;17(12):965-70.

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Primary Hyperoxaluria – Oxlumo Prior Authorization Policy
- Oxlumo™ (lumasiran subcutaneous injection – Alnylam)

REVIEW DATE: 11/01/2023

OVERVIEW

Oxlumo is a hydroxyacid oxidase 1 (*HAO1*)-directed small interfering RNA indicated for the treatment of **primary hyperoxaluria type 1** to lower urinary and plasma oxalate levels in pediatric and adult patients.[1]

Disease Overview

Primary hyperoxaluria type 1 is a rare autosomal recessive inborn error of glyoxylate metabolism that results in the overproduction of oxalate, which forms insoluble calcium oxalate crystals that accumulate in the kidney and other organs, leading to issues such as nephrocalcinosis, formation of renal stones, and renal impairment.[2] Mutations in the alanine:glyoxylate aminotransferase gene (AGXT) cause primary hyperoxaluria type 1.[3] Liver transplantation is the only curative intervention for primary hyperoxaluria type 1 as it corrects the underlying enzymatic defect due to mutations of the AGXT gene.[2-4]

Clinical Efficacy

The efficacy of Oxlumo for the treatment of primary hyperoxaluria type 1 has been evaluated in three pivotal studies.[1,5,6,7] One study included patients ≥ 6 years of age with confirmed AGXT mutations and urinary oxalate excretion ≥ 0.7 mmol/24 hr/1.73 m^2.[5] A second, single-arm study included patients < 6 years of age with a genetically-confirmed primary hyperoxaluria type 1 diagnosis and an elevated spot urinary oxalate:creatinine ratio for age/weight.[6] Efficacy in regard to the urinary oxalate:creatinine ratio was evaluated at Month 6. A third clinical trial evaluated patients of any age with genetically-confirmed primary hyperoxaluria type 1 and a plasma oxalate level ≥ 20 µmol/L.[7] The primary efficacy endpoint of the mean reduction in plasma oxalate was assessed following 6 months of Oxlumo therapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Oxlumo. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Oxlumo as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Oxlumo to be prescribed by or in consultation with a physician who specializes in the condition being treated. All reviews will be forwarded to the Medical Director for evaluation.

Documentation: Documentation is required for use of Oxlumo as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information. Subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *Oxlumo Prior Authorization Policy* through the Coverage Review Department, and who is requesting reauthorization, the criteria utilized do NOT require re-submission of documentation for reauthorization, except for the criterion requiring documentation of a continued benefit from Oxlumo therapy.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Oxlumo is recommended in those who meet the following criteria:

FDA-Approved Indication

150. Primary Hyperoxaluria Type 1. Approve Oxlumo for the duration noted if the patient meets one of the following criteria (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, and iv):

i. Patient has had a genetic test confirming the diagnosis of Primary Hyperoxaluria Type 1 via identification of an alanine:glyoxylate aminotransferase gene (AGXT) mutation **[documentation required]**; AND

ii. Patient meets ONE of the following (a, b, or c):

a) Patient has a urinary oxalate excretion ≥ 0.7 mmol/24 hours/1.73 m^2 **[documentation required]**; OR

b) Patient has a urinary oxalate:creatinine ratio above the age-specific upper limit of normal **[documentation required]**; OR

c) Patient has a plasma oxalate level ≥ 20 µmol/L **[documentation required]**; AND

iii. Patient has not previously received a liver transplant for Primary Hyperoxaluria Type 1; AND

iv. The medication is prescribed by or in consultation with a nephrologist or urologist.

B) Patient is Currently Receiving Oxlumo. Approve for 1 year if, according to the prescriber, the patient is continuing to derive benefit from Oxlumo as determined by the most recent (i.e., within the past 6 months) objective measurement **[documentation required]**.

Note: Examples of objective measurements of a response to Oxlumo therapy are reduced urinary oxalate excretion, decreased urinary oxalate:creatinine ratio, or reduced plasma oxalate levels from baseline (i.e., prior to Oxlumo therapy) or improved or stabilized clinical signs/symptoms of Primary Hyperoxaluria Type 1 (e.g., nephrocalcinosis, formation of renal stones, renal impairment).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Oxlumo is not recommended in the following situations:

213. Primary Hyperoxaluria Type 2 (PH2). Oxlumo is not expected to be effective for the treatment of PH2, because its mechanism of action does not affect the metabolic pathways causing hyperoxaluria in PH2.[1] Oxlumo has not been studied for the treatment of patients with PH2.

214. Primary Hyperoxaluria Type 3 (PH3). Oxlumo is not expected to be effective for the treatment of PH3, because its mechanism of action does not affect the metabolic pathways causing hyperoxaluria in PH3.[1] Oxlumo has not been studied for the treatment of patients with PH3.

215. Concurrent use of Oxlumo with Rivfloza (nedosiran subcutaneous injection). Rivfloza is another small interfering RNA agent and should not be used with Oxlumo.

216. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

667. Oxlumo™ subcutaneous injection [prescribing information]. Cambridge, MA: Alnylam; October 2022.
668. Milliner DS, Harris PC, Cogal AG, et al. Primary Hyperoxaluria Type 1. Gene Reviews® Available at: https://www.ncbi.nlm.nih.gov/books/NBK1283/. Updated February 10, 2022. Accessed on September 14, 2023.
669. Primary Hyperoxaluria: MedlinePlus Genetics. U.S. National Library of Medicine; National Institutes of Health; Department of Health and Human Services. Available at: https://medlineplus.gov/genetics/condition/primary-hyperoxaluria/#resources. Updated November 8, 2021. Accessed on September 14, 2023.
670. Cochat P, Rumsby G. Primary hyperoxaluria. *N Engl J Med*. 2013;369(7):649-658.
671. Garrelfs SF, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria Type 1. *N Engl J Med*. 2021;384(13):1216-1226.
672. Sas DJ, Magen D, Hayes W, et al. Phase 3 trial of lumasiran for primary hyperoxaluria type 1: a new RNAi therapeutic in infants and young children. *Genet Med*. 2022;24(3):654-662.
673. Michael M, Groothoff JW, Shasha-Lavsky H, et al. Lumasiran for advanced primary hyperoxaluria type 1: phase 3 ILLUMINATE-C. *Am J Kidney Dis*. 2022 July 14. [Epub ahead of print].

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Primary Hyperoxaluria Medications – Rivfloza Prior Authorization Policy

- Rivfloza™ (nedosiran subcutaneous injection – Novo Nordisk)

REVIEW DATE: 11/22/2023

OVERVIEW

Rivfloza, a lactate dehydrogenase A-directing (LDHA) small interfering RNA, is indicated for the treatment of **primary hyperoxaluria type 1** (PH1) to lower urinary and plasma oxalate levels in adults and children ≥ 9 years of age with relatively preserved kidney function.[1]

Disease Overview

Primary hyperoxaluria type 1 is a rare autosomal recessive inborn error of glyoxylate metabolism that results in the overproduction of oxalate, which forms insoluble calcium oxalate crystals that accumulate in the kidney and other organs, leading to issues such as nephrocalcinosis, formation of renal stones, and renal impairment.[2] Mutations in the alanine:glyoxylate aminotransferase gene (AGXT) cause primary hyperoxaluria type 1.[3] Liver transplantation is the only curative intervention for primary hyperoxaluria type 1 as it corrects the underlying enzymatic defect due to mutations of the AGXT gene.[2-4]

Clinical Efficacy

The efficacy of Rivfloza for the treatment of primary hyperoxaluria type 1 has been evaluated in one pivotal study.[1,5] The study included patients ≥ 9 years of age with genetically confirmed PH1 and urinary oxalate excretion ≥ 0.7 mmol/24 hr/1.73 m^2. An ongoing open-label extension trial is following patients for up to 4 years.[6] The primary efficacy endpoint of the area under the curve (AUC) percent change from baseline in 24-hour urinary oxalate excretion was assessed following 6 months of Rivfloza therapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Rivfloza. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Rivfloza as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Rivfloza to be prescribed by or in consultation with a physician who specializes in the condition being treated. All reviews will be forwarded to the Medical Director for evaluation.

Documentation: Documentation is required for use of Rivfloza as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information. Subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the Rivfloza *Prior Authorization Policy* through the Coverage Review Department, and who is requesting reauthorization, are NOT required to re-submit documentation for reauthorization, except for the criterion requiring documentation of a continued benefit from Rivfloza therapy.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rivfloza is recommended in those who meet the following criteria:

FDA-Approved Indication

151. Primary Hyperoxaluria Type 1. Approve Rivfloza for the duration noted if the patient meets one of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, iv, v, and vi):

i. Patient is ≥ 9 years of age; AND

ii. Patient has had a genetic test confirming the diagnosis of Primary Hyperoxaluria Type 1 via identification of an alanine:glyoxylate aminotransferase gene (AGXT) mutation **[documentation required]**; AND

iii. Patient has an estimated glomerular filtration rate (eGFR) ≥ 30 ml/min per 1.73 m^2 **[documentation required]**; AND

iv. Patient meets ONE of the following (a, b, or c):

a) Patient has a urinary oxalate excretion ≥ 0.7 mmol/24 hours/1.73 $meters^2$ **[documentation required]**; OR

b) Patient has a urinary oxalate:creatinine ratio above the age-specific upper limit of normal **[documentation required]**; OR

c) Patient has a plasma oxalate level ≥ 20 µmol/L **[documentation required]**; AND

v. Patient has not previously received a liver transplant for Primary Hyperoxaluria Type 1; AND

vi. The medication is prescribed by or in consultation with a nephrologist or urologist.

B) Patient is Currently Receiving Rivfloza. Approve for 1 year if, according to the prescriber, the patient is continuing to derive benefit from Rivfloza as determined by the most recent (i.e., within the past 6 months) objective measurement **[documentation required]**.

Note: Examples of objective measurements of a response to Rivfloza therapy are reduced urinary oxalate excretion, decreased urinary oxalate:creatinine ratio, or reduced plasma oxalate levels from baseline (i.e., prior to Rivfloza therapy) or improved or stabilized clinical signs/symptoms of Primary Hyperoxaluria Type 1 (e.g., nephrocalcinosis, formation of renal stones, renal impairment).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rivfloza is not recommended in the following situations:

217. Primary Hyperoxaluria Type 2 (PH2). Rivfloza may have benefit in PH2; however, the efficacy and safety of Rivfloza in patients with PH2 have not been established. Clinical trials are ongoing.

218. Primary Hyperoxaluria Type 3 (PH3). Rivfloza may have benefit in PH3; however, the efficacy and safety of Rivfloza in patients with PH3 have not been established. Clinical trials are ongoing.

219. Primary Hyperoxaluria with end stage renal disease (ESRD). Rivfloza may have benefit in patients with PH1 or PH2 and ESRD; however, the efficacy and safety of Rivfloza in this patient population have not been established. Clinical trials are ongoing.

220. Concurrent use of Rivfloza with Oxlumo (lumasiran subcutaneous injection). Oxlumo is another small interfering RNA agent and should not be used with Rivfloza.

221. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

674. Rivfloza™ subcutaneous injection [prescribing information]. Plainsboro, NJ: Novo Nordisk; September 2023.
675. Milliner DS, Harris PC, Sas DJ, et al. Primary Hyperoxaluria Type 1. Gene Reviews® Available at: https://www.ncbi.nlm.nih.gov/books/NBK1283/#:~:text=In%20primary%20hyperoxaluria%20type%201,deposit%20in%20the%20renal%20parenchyma. Updated February 10, 2022. Accessed on October 3, 2023.
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677. Cochat P, Rumsby G. Primary hyperoxaluria. *N Engl J Med*. 2013;369(7):649-658.
678. Baum MA, Langman C, Cochat P, et al. PHYOX2: a pivotal randomized study of nedosiran in primary hyperoxaluria type 1 or 2. *Kidney Int*. 2023;103(1):207-217.
679. Hoppe B, Coenen M, Schalk G, et al. Nedosiran in primary hyperoxaluria subtype 1: interim results from an open label extension trial (PHYOX3) [poster]. Presented at: 19th International Pediatric Nephrology Association (IPNA) Congress. Calgary, Canada. September 7-11, 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Tiopronin Products Prior Authorization Policy
- Thiola® (tiopronin tablets – Mission Pharmacal, generic)
- Thiola® EC (tiopronin delayed-release tablets – Mission Pharmacal)

REVIEW DATE: 10/25/2023

OVERVIEW

Tiopronin tablets (Thiola, generic) and Thiola EC are indicated, in combination with high fluid intake, alkali, and diet modification, for the prevention of cystine kidney stone formation in adults and pediatric patients ≥ 20 kg with severe homozygous **cystinuria**, who are not responsive to these measures alone.[1,2]

Disease Overview

40. Cystinuria is an autosomal recessive disorder of abnormal cystine transport.[3] The estimated prevalence is 1:7,000 to 1:10,000 individuals in the US. Excessive undissolved cystine in the urine leads to formation of stones in the kidney, bladder, and/or ureter. Symptoms typically begin to manifest between 10 and 30 years of age, although elevated cystine excretion may be found in infancy. Diagnosis is made clinically based on quantitative urinary cystine assays; genetic testing is not routine as it does not change medical management.[4] Homozygotes exhibit urinary cystine excretion > 300 to 400 mg/L/day, whereas heterozygotes have intermediate urinary cystine excretion. Treatment is directed at decreasing urinary cystine concentration (generally targeting a urine cystine < 250 mg/L) and enhancing solubility.[4,5] Tiopronin products work by binding to cystine and increasing urinary solubility.[4]

41.

42. Guidelines

According to the American Urological Association guideline for medical management of kidney stones (2014, confirmed 2019), all patients with cystine kidney stones should be encouraged to drink large amounts of fluid to maintain low urinary cystine concentrations; often volumes of 4 liters per day are required.[5] Recommended dietary modifications include restriction of sodium and animal proteins. Alkalization of urine is also used to improve cystine solubility. This can be achieved through increased fruit and vegetable intake and/or with medications such as potassium citrate. The guideline recommends tiopronin for patients with cystine kidney stones who are unresponsive to increased fluid intake, dietary modification, and urinary alkalization. Captopril, another thiol agent, has not been shown to be effective for the prevention of recurrent cystine stones. D-penicillamine may be associated with more adverse events and is not preferred.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of tiopronin products. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with tiopronin products, approval requires the requested medication to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of tiopronin products is recommended in those who meet the following criteria:

FDA-Approved Indication

12. **Cystinuria.** Approve for 1 year if the patient meets the following (A, B, C, and D):

G) Patient weighs ≥ 20 kg; AND

H) Diagnosis of cystinuria has been confirmed based on laboratory testing (e.g., urinary cystine crystals present on microscopy, quantitative urine cystine assay); AND

I) According to the prescriber, the patient has had an inadequate response to high fluid intake, dietary modification, and urinary alkalization; AND

J) The medication is prescribed by or in consultation with a nephrologist, urologist, or physician who specializes in the treatment of cystinuria.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of tiopronin products is not recommended in the following situations:

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

178. Thiola® tablets [prescribing information]. San Antonio, TX: Mission Pharmacal; June 2019.
179. Thiola® EC delayed-release tablets [prescribing information]. San Antonio, TX: Mission Pharmacal; March 2021.
180. Cystinuria. National Organization for Rare Disorders. Updated 2020. Available at: https://rarediseases.org/rare-diseases/cystinuria/. Accessed on October 10, 2023.
181. Castro Pereira DJ, Schoolwerth AC, Pais VM. Cystinuria: current concepts and future directions. *Clin Nephrology.* 2015;83(3):138-146.
182. Pearle MS, Goldfarb DS, Assimos DG, et al. American Urological Association. Medical management of kidney stones: AUA guideline. *J Urol.* 2014;192(2):316-24.

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Xuriden Prior Authorization Policy
- Xuriden® (uridine triacetate oral granules – Wellstat Therapeutics)

REVIEW DATE: 08/16/2023

OVERVIEW

Xuriden, a pyrimidine analog for uridine replacement, is indicated for the treatment of **hereditary orotic aciduria** in adults and pediatric patients.[1]

Disease Overview

43. Hereditary orotic aciduria, also known as orotic aciduria type 1, is an extremely rare, autosomal recessive genetic disorder of pyrimidine metabolism.[1-3] It is estimated to affect less than 1:1,000,000 live births. Only about 20 cases have been reported in the medical literature. In hereditary orotic aciduria, a mutation in the *UMPS* gene leads to defective uridine 5'monophosphate synthase. Deficiency in this enzyme prevents the last two steps in pyrimidine biosynthesis, leading to inadequate levels of uridine monophosphate and excess levels of orotic acid (a uridine precursor). Because the condition is so rare, hereditary orotic aciduria is not fully understood. Affected infants may develop megaloblastic anemia, developmental delays, or failure to thrive. Orotic acid crystals in the urine can lead to urinary obstruction. Xuriden replaces uridine in the circulation, and as a result of feedback inhibition, overproduction of orotic acid is reduced. Diagnosis is made by detailed patient and family as well as thorough clinical evaluation and examination of urine. Most individuals have their diagnosis confirmed through molecular genetic testing; however, this is only available at specialized laboratories.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Xuriden. Because of the specialized skills required for evaluation and diagnosis of patients treated with Xuriden, approval requires the requested medication to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xuriden is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Hereditary Orotic Aciduria (Orotic Aciduria Type 1).** Approve for 1 year if the patient meets the following (A and B):
1. Patient has hereditary orotic aciduria confirmed by at least one of the following (i or ii):
1. Molecular genetic testing confirming biallelic pathogenic mutations in the *UMPS* gene; OR
1. Clinical diagnosis supported by all of the following (a, b, and c):
1. At least one clinical manifestation consistent with orotic aciduria type 1; AND

   Note: Examples of clinical manifestations include megaloblastic anemia, immunodeficiency, developmental delays, and failure to thrive.

1. First-degree family relative (i.e., parent or sibling) with hereditary orotic aciduria; AND
1. Urinary orotic acid level above the normal reference range for the reporting laboratory; AND
1. Xuriden is prescribed by, or in consultation with, a metabolic specialist, geneticist, or physician specializing in the condition being treated.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xuriden is not recommended in the following situations:

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

183. Xuriden® oral granules [prescribing information]. Rockville, MD: Wellstat Therapeutics; December 2019.
184. Hereditary orotic aciduria. National Organization for Rare Disorders. Updated 2018. Available at: https://rarediseases.org/rare-diseases/hereditary-orotic-aciduria/. Accessed on August 1, 2023.
185. Orotic aciduria type 1. Genetic and Rare Diseases Information Center. Updated November 8, 2021. Available at: https://rarediseases.info.nih.gov/diseases/5429/hereditary-orotic-aciduria. Accessed on August 1, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Cysteamine (Oral) Products Prior Authorization Policy
- Cystagon® (cysteamine bitartrate capsules – Mylan)
- Procysbi® (cysteamine bitartrate delayed-release capsules, delayed release granules – Horizon)

REVIEW DATE: 03/29/2023

OVERVIEW

Cystagon and Procysbi are cystine-depleting agents indicated for the management of **nephropathic cystinosis**.[1-2] Note that Procysbi is indicated specifically in patients who are ≥ 1 year of age, whereas there is not an age limit for pediatric use of Cystagon.

Therapy with a cysteamine product should be initiated promptly once the diagnosis is confirmed (i.e., increased white blood cell cystine concentration).

Disease Overview

Cystinosis is a very rare autosomal recessive inborn error of metabolism in which cystine accumulates within lysosomes and forms crystals in many tissues, including the kidneys, liver, bone marrow, pancreas, muscle, rectal mucosa, brain, and eye.[3,4] Patients with cystinosis also experience growth failure and rickets, and cystine deposits in the cornea cause photophobia. Over time, most organs are damaged. Diagnosis is confirmed by measuring cystine levels in polymorphonuclear leukocytes.[5] Molecular genetic testing identifies a characteristic mutation of the *CTNS* gene.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of oral cysteamine products. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with oral cysteamine products as well as the monitoring required for adverse events and long-term efficacy, approval requires oral cysteamine products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of oral cysteamine products is recommended in those who meet the following criteria:

FDA-Approved Indication

152. Cystinosis, Nephropathic. Approve for 1 year if the patient meets the following (A, B, and C):
- **A)** According to the prescriber, diagnosis was confirmed by one of the following (i or ii):
  - **i.** Genetic testing confirmed a mutation of the *CTNS* gene; OR
  - **ii.** White blood cell cystine concentration above the upper limit of the normal reference range for the reporting laboratory; AND

Note: The methods used for measuring cystine vary among individual laboratories and depend upon the assay method used by the individual laboratory; values obtained from using different assay methods may not be interchangeable.

B) Patient will not be using Cystagon and Procysbi concurrently; AND

C) The medication is prescribed by or in consultation with a nephrologist or a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of oral cysteamine products is not recommended in the following situations:

222. Concomitant Therapy with Cystagon and Procysbi. There are no data available to support concomitant use.

223. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

680. Procysbi® [prescribing information]. Lake Forest, IL: Horizon; February 2022.
681. Cystagon® [prescribing information]. Morgantown, WV: Mylan; January 2019.
682. Wilmer MJ, Schoeber JP, van den Heuvel LP, Levtchenko EN. Cystinosis: practical tools for diagnosis and treatment. *Pediatr Nephrol*. 2011; 26(2): 205–215.
683. Elmonem MA, Veys KR, Soliman NA, et al. Cystinosis: a review. *Orphanet J Rare Dis*. 2016 Apr 22;11:47.
684. National Organization for Rare Disorders (NORD). Cystinosis. Accessed on March 4, 2023. Available at: https://rarediseases.org/rare-diseases/cystinosis/.

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Cysteamine Ophthalmic Solution Prior Authorization Policy
- Cystadrops® (cysteamine 0.37% ophthalmic solution – Recordati Rare Diseases)
- Cystaran® (cysteamine 0.44% ophthalmic solution – Leadiant Biosciences)

REVIEW DATE: 03/29/2023

OVERVIEW

Cystamine ophthalmic solution is a cystine-depleting agent indicated for the treatment of **corneal cystine crystal accumulation in patients with cystinosis**.[1,2]

Disease Overview

Cystinosis is a rare autosomal recessive inborn error of metabolism in which cystine accumulates within lysosomes and forms crystals in many tissues, including the kidneys, liver, bone marrow, pancreas, muscle, rectal mucosa, brain, and eye.[3] Cystine deposits in the cornea cause photophobia. Patients may present only with corneal crystal deposition but no associated systemic manifestations; the kidney, retina, and other organs are free of cystine accumulation in these patients. In patients without systemic symptoms, diagnosis of ocular cystinosis is often in adulthood when corneal crystal deposits are noted on ocular examination.[4] Of note, with oral cysteamine the concentration obtained in corneal tissue is inadequate and does not affect corneal cystine crystals. Topical treatment is required to dissolve existing cystine crystals.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of cysteamine ophthalmic solution. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with cysteamine ophthalmic solution as well as the monitoring required for adverse events and long-term efficacy, approval requires cysteamine ophthalmic solution to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of cysteamine ophthalmic solution is recommended in those who meet the following criteria:

FDA-Approved Indication

153. Cystinosis, Corneal Cysteine Crystal Deposits. Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient has corneal cysteine crystal deposits confirmed by slit-lamp examination; AND
- **B)** The medication is prescribed by or in consultation with an ophthalmologist or a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of cysteamine ophthalmic solution is not recommended in the following situations:

224. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Phenylbutyrate Products Prior Authorization Policy
- Buphenyl® (sodium phenylbutyrate tablets and powder for oral solution – Horizon, generic)
- Olpruva® (sodium phenylbutyrate for oral suspension – Acer)
- Pheburane® (sodium phenylbutyrate oral pellets – Medunik)
- Ravicti® (glycerol phenylbutyrate oral liquid – Horizon)

REVIEW DATE: 03/29/2023; selected revision 07/12/2023

OVERVIEW

Phenylbutyrate products are indicated in combination with dietary management for treatment of **urea cycle disorders (UCDs)**.

- **Sodium phenylbutyrate** products are indicated as adjunctive therapy in the chronic management of adult and pediatric patients with UCDs involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS).[1-3]
  - **Buphenyl** and **Pheburane** can be administered orally in pediatric patients weighing less than 20 kg.
  - Buphenyl powder is compatible with feeding tube administration.
  - **Olpruva** is indicated for use in patients weighing $\geq$ 20 kg and with a body surface area of ≥ 1.2 m^2.

  Limitation of use: Sodium phenylbutyrate products are not indicated for the treatment of acute hyperammonemia, which can be a life-threatening medical emergency that requires rapid acting interventions to reduce plasma ammonia levels.
- **Ravicti** is indicated for the chronic management of patients with UCDs involving deficiencies of CPS, OTC, or AS that cannot be managed by dietary protein restriction and/or amino acid supplementation alone.[4]

  Limitation of use: Ravicti is not indicated for treatment of acute hyperammonemia in patients with UCDs. Safety and efficacy for treatment of N-acetylglutamate synthetase deficiency has not been established.

Disease Overview

UCDs are rare inborn errors of metabolism which result from mutations in the genes encoding for enzymes necessary for normal function of the urea cycle: arginase, AS, N-acetyl glutamate synthetase, OTC, and CPS.[5,6] These defects lead to increased amounts of ammonia in the blood which may cause disturbed brain function and severe brain damage. Signs of disease include decreased mental awareness, vomiting, combativeness, slurred speech, unstable gait, and unconsciousness. Diagnosis begins with a clinical suspicion of hyperammonemia.[7] Typically, patients have normal glucose and electrolyte levels. Enzymatic diagnosis and/or genetic testing is also available; however, treatment should not be delayed while waiting for a final diagnosis. Most deaths have occurred during an episode of acute hyperammonemic encephalopathy.[5,6] Treatment includes use of alternative waste nitrogen excretion pathways (e.g., Buphenyl, Ravicti); other treatments may include hemodialysis, dietary protein restriction, and, in some cases, essential amino acid supplementation.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of phenylbutyrate products. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with phenylbutyrate products as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of phenylbutyrate products is recommended in those who meet the following criteria:

FDA-Approved Indication

154. Urea Cycle Disorders. Approve for the duration noted if the patient meets ALL of the following (A, B, C, and D):
Note: Examples include deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase, or argininosuccinic acid synthetase.

- **A)** According to the prescriber, the diagnosis was confirmed by one of the following (i or ii):
  - **i.** Approve for 1 year if genetic testing confirmed a mutation resulting in a urea cycle disorder; OR
  - **ii.** Approve for 3 months if the patient has hyperammonemia diagnosed with an ammonia level above the upper limit of the normal reference range for the reporting laboratory; AND
    Note: Reference ranges are dependent upon patient's age.
- **B)** The medication is prescribed in conjunction with a protein-restricted diet; AND
- **C)** Patient will not be receiving concurrent therapy with another phenylbutyrate product; AND
  Note: Examples of phenylbutyrate products that should not be taken concurrently include sodium phenylbutyrate (Buphenyl, generic), Pheburane, Olpruva, and Ravicti.
- **D)** The medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of phenylbutyrate products is not recommended in the following situations:

225. Concomitant Therapy with Another Phenylbutyrate Product. There are no data available to support concomitant use.
Note: Examples of phenylbutyrate products include sodium phenylbutyrate, Olpruva, Pheburane, and Ravicti.

226. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Methylergonovine Prior Authorization Policy
- Methergine® (methylergonovine maleate tablets – Lupin, generic)

REVIEW DATE: 06/07/2023

OVERVIEW

Methylergonovine, a semi-synthetic ergot alkaloid, is indicated for management of **uterine atony, hemorrhage, and subinvolution of the uterus following delivery of the placenta;** and for control of **uterine hemorrhage** in the second stage of labor following delivery of the anterior shoulder.[1]

Other Uses with Supportive Evidence

The National Headache Foundation notes that methylergonovine can cause constriction of the smooth muscles in the blood vessels and this effect can be helpful in treating vascular headaches, such as migraines or cluster headaches.[2] Although methylergonovine is more commonly used for prevention of migraine headaches, it can be taken for acute attacks. However, methylergonovine should only be used for limited periods of time in most patients and only under careful supervision of a physician. The dose of methylergonovine used for migraines is 0.2 to 0.4 mg three times a day; a maximum dose of 1.6 mg/day has been reported (eight 0.2 mg tablets per day).[3]

Guidelines/Recommendations

An updated assessment of the **preventive and acute treatment of migraine** by the **American Headache Society** (AHS) [2018; update 2021] reaffirms previous migraine guidelines.[4,5] Methylergonovine is not addressed in the update. ***Prevention.*** Patients with migraine should be considered for preventive treatment in the following situations: when attacks significantly interfere with patients' daily routines despite acute treatment; frequent attacks (≥ 4 monthly headache days); contraindication to, failure, overuse, or adverse events with acute treatments; or patient preference. Before developing a preventive treatment plan, the appropriate use (e.g., drug type, route and timing of administration, frequency) of acute treatments should be initiated and coupled with education and lifestyle modifications. All patients with migraine should be offered a trial of acute treatment. Based on the level of evidence for efficacy and the American Academy of Neurology scheme for classification of evidence, the following oral treatments have established efficacy and should be offered for migraine prevention: antiepileptic drugs (divalproex sodium, valproate sodium, topiramate [not for women of childbearing potential without a reliable method of birth control]); beta-blockers (metoprolol, propranolol, timolol); and frovatriptan (for short-term preventive treatment of menstrual migraine). The following treatments are probably effective and should be considered for migraine prevention: antidepressants (amitriptyline, venlafaxine); beta-blockers (atenolol, nadolol); and angiotensin receptor blockers (candesartan). ***Treatment.*** Triptans (e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) are considered the gold standard for acute treatment of moderate to severe migraine headaches or mild to moderate migraine headaches that respond poorly to over-the-counter analgesics. Nonsteroidal anti-inflammatory drugs (NSAIDs) as a class are mentioned as an option for acute treatment of mild to moderate migraine attacks; celecoxib is not specifically addressed. The potential for cardiovascular and gastrointestinal adverse events with NSAID use is noted. Other treatment options in the mild to moderate setting include nonopioid analgesics, acetaminophen, or caffeinated analgesic combinations. For moderate to severe attacks or attacks which respond poorly to NSAIDs or caffeinated combinations, the update lists the triptans, dihydroergotamine, the oral calcitonin gene-related peptide (CGRP) receptor antagonists (Nurtec® ODT [rimegepant orally disintegrating tablets,] and Ubrelvy® [ubrogepant tablets]), and Reyvow™ (lasmiditan tablet) as effective

treatments. The recommendation remains that clinicians must consider medication efficacy and potential medication-related adverse events when prescribing acute medications for migraine.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of methylergonovine, for prescriptions with quantities exceeding 28 tablets per 30 days. Twenty-eight (28) tablets per month will be sufficient to treat uterine atony, hemorrhage, and subinvolution of the uterus following the delivery of the placenta (FDA-approved indication). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients with migraines who are treated with methylergonovine as well as the monitoring required for adverse events and long-term efficacy, approval requires methylergonovine to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: Methylergonovine prescriptions for ≤ 28 tablets (0.2 mg strength) per 30 days are excluded from Prior Authorization (PA). The PA policy will only apply to methylergonovine prescriptions with quantities exceeding 28 tablets per 30 days.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of methylergonovine is recommended in those who meet one of the following criteria:

FDA-Approved Indication

4. **Uterine Atony, Hemorrhage, and Subinvolution of the Uterus. Do not approve. The initial quantity of 28 tablets is sufficient to treat this condition; quantities > 28 tablets for this indication will not be approved.**

Other Uses with Supportive Evidence

5. **Migraine Headaches – Acute Treatment.** Approve for 1 year if the patient meets BOTH of the following criteria (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets one of the following (i or ii):
     - **i.** Patient is already receiving methylergonovine therapy; OR
     - **ii. Patient meets the following criteria** (a, b, and c):
       - **a)** Patient has tried and had inadequate efficacy and/or unacceptable side effects to at least one triptan therapy; AND
         Note: Examples of triptans are almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan.
       - **b)** Patient has tried and had inadequate efficacy and/or unacceptable side effects to at least one other type of abortive therapy; AND
         Note: Examples of abortive therapies include analgesics (acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs]), butalbital-containing products (butalbital-acetaminophen, butalbital-acetaminophen-caffeine, butalbital-acetaminophen-caffeine-codeine, butalbital-aspirin-caffeine, butalbital-aspirin-caffeine-codeine), dihydroergotamine (DHE, Migranal, generic), oral calcitonin gene-related peptide (CGRP) receptor antagonists (Nurtec ODT [rimegepant orally disintegrating tablets], Ubrelvy [ubrogepant tablets], Reyvow [lasmiditan tablet]).

c) The medication is prescribed by or in consultation with a neurologist or headache specialist.

6. Migraine Headaches – Prevention. Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) Patient is ≥ 18 years of age: AND

B) Patient has tried at least two standard prophylactic pharmacologic therapies, each from a different pharmacologic class; AND

Note: Examples of prophylactic pharmacologic therapies include angiotensin receptor blocker, angiotensin converting enzyme inhibitor, anticonvulsant, beta-blocker, calcium channel blocker, tricyclic antidepressant, other antidepressant.

C) The medication is prescribed by or in consultation with a neurologist or headache specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of methylergonovine is not recommended in the following situations:

69. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Migraine – Calcitonin Gene-Related Peptide Inhibitors – Aimovig Prior Authorization Policy

- Aimovig® (erenumab-aooe subcutaneous injection – Amgen)

REVIEW DATE: 05/24/2023; selected revision 08/02/2023

OVERVIEW

Aimovig, a calcitonin gene-related peptide (CGRP) receptor antagonist, is indicated for the **preventive treatment of migraine** in adults.[1]

Disease Overview

Migraines have been defined as chronic or episodic. Chronic migraine is described by the International Headache Society as headache occurring on ≥ 15 days/month for > 3 months and has the features of migraine headache on ≥ 8 days/month.[2] Episodic migraine is characterized by headaches that occur < 15 days/month.[3,4] Episodic migraine is more common than chronic migraine; however, chronic migraine is associated with a markedly greater personal and societal burden.

Guidelines

An updated assessment of the **preventive and acute treatment of migraine** by the **American Headache Society** (AHS) [2018; update 2021] reaffirms previous migraine guidelines.[5,6] Patients with migraine should be considered for preventive treatment in the following situations: when attacks significantly interfere with patients' daily routines despite acute treatment; frequent attacks (≥ 4 monthly headache days); contraindication to, failure, overuse, or adverse events with acute treatments; or patient preference. Before developing a preventive treatment plan, the appropriate use (e.g., drug type, route and timing of administration, frequency) of acute treatments should be initiated and coupled with education and lifestyle modifications. All patients with migraine should be offered a trial of acute treatment. Based on the level of evidence for efficacy and the American Academy of Neurology scheme for classification of evidence, the following oral treatments have established efficacy and should be offered for migraine prevention: antiepileptic drugs (**divalproex sodium, valproate sodium, topiramate** [not for women of childbearing potential without a reliable method of birth control]); beta-blockers (**metoprolol, propranolol, timolol**); and **frovatriptan** (for short-term preventive treatment of menstrual migraine). The following treatments are probably effective and should be considered for migraine prevention: antidepressants (**amitriptyline, venlafaxine**); beta-blockers (**atenolol, nadolol**); and angiotensin receptor blockers (**candesartan**). Additionally, the following treatments are possibly effective and can be considered for migraine prevention: calcium channel blockers (e.g., **verapamil**) and angiotensin converting enzyme inhibitors (e.g., **lisinopril**).[14,15]

Five injectable preventive therapies for migraine are mentioned in the AHS consensus statement: Botox® (onabotulinumtoxinA subcutaneous injection) and four monoclonal antibodies targeting CGRP (Aimovig, Ajovy® [fremanezumab-vfrm subcutaneous injection], Emgality® [galcanezumab-gnlm subcutaneous injection], and Vyepti® [eptinezumab-jjmr intravenous infusion]).[5,6] The update notes that a CGRP inhibitor should only be initiated in patients who are diagnosed with migraine, have ≥ 4 migraine headache days/month, and have intolerance or inadequate response to 6-week trials of at least two traditional oral migraine preventive medications. Additional criteria apply depending on the number and severity of monthly headache days. Clinical judgment may result in an emerging treatment being added to one or more established treatments. If initiating treatment with a CGRP inhibitor in a patient already on a preventive

treatment, it is appropriate to add the CGRP inhibitor to the existing regimen and make no other changes until the effectiveness of the CGRP inhibitor is determined since the risk of interactions between traditional oral migraine preventive medications and the CGRP inhibitors is minimal or nonexistent. Making a decision regarding continuation of therapy for a CGRP inhibitor requires a trial of the medication for ≥ 3 months for those administered monthly and ≥ 6 months for those administered quarterly. Treatment should be continued only if benefits can be documented during that time (e.g., reduction in mean monthly headache days of ≥ 50% relative to the pretreatment baseline) or a meaningful improvement on a validated migraine-specific patient-reported outcome measure. Since migraine may improve or remit over time, it is important to re-evaluate the therapeutic response and, if possible, taper or discontinue treatment if patient no longer meets the criteria for offering preventive treatment. However, once control is established, the decision to discontinue or taper treatment should be a shared decision between the patient and clinician.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Aimovig. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Aimovig is recommended in those who meet the following criteria:

FDA-Approved Indication

52. Migraine Headache Prevention. Approve for 1 year if the patient meets the following (A, B, C, D, and E):

29. Patient is ≥ 18 years of age; AND

30. Patient has ≥ 4 migraine headache days per month (prior to initiating a migraine-preventive medication); AND

31. Patient has tried at least two standard prophylactic (preventive) pharmacologic therapies, each from a different pharmacologic class; AND

Note: Standard prophylactic (preventive) pharmacologic therapies include angiotensin receptor blocker, angiotensin converting enzyme inhibitor, anticonvulsant, beta-blocker, calcium channel blocker, tricyclic antidepressant, other antidepressant. A patient who has already tried an oral or injectable calcitonin gene-related peptide (CGRP) inhibitor indicated for the prevention of migraine or Botox (onabotulinumtoxinA injection) for the prevention of migraine is not required to try two standard prophylactic pharmacologic therapies.

32. Patient meets ONE of the following (i, ii, or iii):

a) Patient has had inadequate efficacy to both of those standard prophylactic (preventive) pharmacologic therapies, according to the prescriber; OR

b) Patient has experienced adverse event(s) severe enough to warrant discontinuation of both of those standard prophylactic (preventive) pharmacologic therapies, according to the prescriber; OR

c) Patient meets BOTH of the following (a and b):

a. Patient has had inadequate efficacy to one standard prophylactic (preventive) pharmacologic therapy; AND

b. Patient has experienced adverse event(s) severe enough to warrant discontinuation to another standard prophylactic (preventive) pharmacologic therapy, according to the prescriber; AND

33. If a patient is currently taking Aimovig, the patient has had a significant clinical benefit from the medication, as determined by the prescriber.
Note: Examples of significant clinical benefit include a reduction in the overall number of migraine days per month or a reduction in number of severe migraine days per month from the time that Aimovig was initiated.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Aimovig is not recommended in the following situations:

1. **Acute Treatment of Migraine.** Aimovig has not been studied for the acute treatment of migraine.

2. **Cluster Headache, Treatment or Prevention.** Clinical data is currently lacking for the use of Aimovig in patients with cluster headache. The pivotal trials of Aimovig excluded patients with this condition.[7,8]

3. **Concurrent use with another calcitonin gene-related peptide (CGRP) inhibitor being prescribed for migraine headache prevention.**
Note: CGRP inhibitors that are indicated for migraine headache prevention include Ajovy (fremanezumab-vfrm subcutaneous injection), Emgality (galcanezumab-gnlm subcutaneous injection), Vyepti (eptinezumab-jjmr intravenous infusion), and Qulipta (atogepant tablets). Aimovig, Ajovy, Emgality, and Vyepti are injectable CGRP inhibitors for migraine prevention and have not been studied for use in combination with another agent in the same class.[9-11] Qulipta is an oral CGRP inhibitor for the preventive treatment of migraine in adults.[12]

4. **Concurrent use with Nurtec ODT (rimegepant sulfate orally disintegrating tablet) when used as a preventive treatment of migraine.** Nurtec ODT is an oral CGRP inhibitor for the acute treatment of migraine and for the preventive treatment of episodic migraine in adults.[13]

5. **Hemiplegic Migraine, Treatment or Prevention.** Aimovig has not been studied in patients with hemiplegic migraine. The pivotal trials of Aimovig excluded patients with this condition.[7,8]

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Migraine – Calcitonin Gene-Related Peptide Inhibitors – Ajovy Prior Authorization Policy
- Ajovy® (fremanezumab-vfrm subcutaneous injection – Teva)

REVIEW DATE: 05/24/2023; selected revision 08/02/2023

OVERVIEW

Ajovy, a calcitonin gene-related peptide (CGRP) antagonist, is indicated for the **preventive treatment of migraine** in adults.[1]

Disease Overview

Migraines have been defined as chronic or episodic. Chronic migraine is described by the International Headache Society as headache occurring on ≥ 15 days/month for > 3 months and has the features of migraine headache on ≥ 8 days/month.[2] Episodic migraine is characterized by headaches that occur < 15 days/month.[3,4] Episodic migraine is more common than chronic migraine; however, chronic migraine is associated with a markedly greater personal and societal burden.

Guidelines

An updated assessment of the **preventive and acute treatment of migraine** by the **American Headache Society** (AHS) [2018; update 2021] reaffirms previous migraine guidelines.[5,6] Patients with migraine should be considered for preventive treatment in the following situations: when attacks significantly interfere with patients' daily routines despite acute treatment; frequent attacks (≥ 4 monthly headache days); contraindication to, failure, overuse, or adverse events with acute treatments; or patient preference. Before developing a preventive treatment plan, the appropriate use (e.g., drug type, route and timing of administration, frequency) of acute treatments should be initiated and coupled with education and lifestyle modifications. All patients with migraine should be offered a trial of acute treatment. Based on the level of evidence for efficacy and the American Academy of Neurology scheme for classification of evidence, the following oral treatments have established efficacy and should be offered for migraine prevention: antiepileptic drugs (**divalproex sodium, valproate sodium, topiramate** [not for women of childbearing potential without a reliable method of birth control]); beta-blockers (**metoprolol, propranolol, timolol**); and **frovatriptan** (for short-term preventive treatment of menstrual migraine). The following treatments are probably effective and should be considered for migraine prevention: antidepressants (**amitriptyline, venlafaxine**); beta-blockers (**atenolol, nadolol**); and angiotensin receptor blockers (**candesartan**). Additionally, the following treatments are possibly effective and can be considered for migraine prevention: calcium channel blockers (e.g., **verapamil**) and angiotensin converting enzyme inhibitors (e.g., **lisinopril**).[13,14]

Five injectable preventive therapies for migraine are mentioned in the AHS consensus statement: Botox® (onabotulinumtoxinA subcutaneous injection) and four monoclonal antibodies targeting CGRP (Aimovig® [erenumab-aooe subcutaneous injection], Ajovy, Emgality® [galcanezumab-gnlm subcutaneous injection], and Vyepti® [eptinezumab-jjmr intravenous infusion]).[5,6] The update notes that a CGRP inhibitor should only be initiated in patients who are diagnosed with migraine, have ≥ 4 migraine headache days/month, and have intolerance or inadequate response to 6-week trials of at least two traditional oral migraine preventive medications. Additional criteria apply depending on the number and severity of monthly headache days. Clinical judgment may result in an emerging treatment being added to one or more established treatments. If initiating treatment with a CGRP inhibitor in a patient already on a preventive treatment, it is appropriate to add the CGRP inhibitor to the existing regimen and make no other changes until the effectiveness of the

CGRP inhibitor is determined since the risk of interactions between traditional oral migraine preventive medications and the CGRP inhibitors is minimal or nonexistent. Making a decision regarding continuation of therapy for a CGRP inhibitor requires a trial of the medication for ≥ 3 months for those administered monthly and ≥ 6 months for those administered quarterly. Treatment should be continued only if benefits can be documented during that time (e.g., reduction in mean monthly headache days of ≥ 50% relative to the pretreatment baseline) or a meaningful improvement on a validated migraine-specific patient-reported outcome measure. Since migraine may improve or remit over time, it is important to re-evaluate the therapeutic response and, if possible, taper or discontinue treatment if patient no longer meets the criteria for offering preventive treatment. However, once control is established, the decision to discontinue or taper treatment should be a shared decision between the patient and clinician.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ajovy. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ajovy is recommended in those who meet the following criteria:

FDA-Approved Indication

53. Migraine Headache Prevention. Approve for 1 year if the patient meets the following (A, B, C, D, and E):

34. Patient is ≥ 18 years of age; AND

35. Patient has ≥ 4 migraine headache days per month (prior to initiating a migraine-preventive medication); AND

36. Patient has tried at least two standard prophylactic (preventive) pharmacologic therapies, each from a different pharmacologic class; AND

Note: Standard prophylactic (preventive) pharmacologic therapies include angiotensin receptor blocker, angiotensin converting enzyme inhibitor, anticonvulsant, beta-blocker, calcium channel blocker, tricyclic antidepressant, other antidepressant. A patient who has already tried an oral or injectable calcitonin gene-related peptide (CGRP) inhibitor indicated for the prevention of migraine or Botox (onabotulinumtoxinA injection) for the prevention of migraine is not required to try two standard prophylactic pharmacologic therapies.

37. Patient meets ONE of the following (i, ii, or iii):

i. Patient has had inadequate efficacy to both of those standard prophylactic (preventive) pharmacologic therapies, according to the prescriber; OR

ii. Patient has experienced adverse event(s) severe enough to warrant discontinuation of both of those standard prophylactic (preventive) pharmacologic therapies, according to the prescriber; OR

iii. Patient meets BOTH of the following (a and b):

a) Patient has had inadequate efficacy to one standard prophylactic (preventive) pharmacologic therapy; AND

b) Patient has experienced adverse event(s) severe enough to warrant discontinuation to another standard prophylactic (preventive) pharmacologic therapy, according to the prescriber; AND

38. If the patient is currently taking Ajovy, the patient has had a significant clinical benefit from the medication, as determined by the prescriber.

Note: Examples of significant clinical benefit include a reduction in the overall number of migraine days per month or a reduction in number of severe migraine days per month from the time that Ajovy was initiated.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ajovy is not recommended in the following situations:

7. **Acute Treatment of Migraine.** Ajovy has not been studied for the acute treatment of migraine.

8. **Cluster Headache, Treatment or Prevention.** Ajovy has not been found to be effective in Phase III clinical trials in patients with episodic and chronic cluster headache.[7]

141.

9. **Concurrent use with another calcitonin gene-related peptide (CGRP) inhibitor being prescribed for migraine headache prevention.**
   Note: CGRP inhibitors that are indicated for migraine headache prevention include Aimovig (erenumab-aooe subcutaneous injection), Emgality (galcanezumab-gnlm subcutaneous injection), Vyepti (eptinezumab-jjmr intravenous infusion), and Qulipta (atogepant tablets). Ajovy, Aimovig, Emgality, and Vyepti are injectable CGRP inhibitors for migraine prevention and have not been studied for use in combination with another agent in the same class.[8-10] Qulipta is an oral CGRP inhibitor for the preventive treatment of migraine in adults.[11]

10. **Concurrent use with Nurtec ODT (rimegepant sulfate orally disintegrating tablet) when used as a preventive treatment of migraine.** Nurtec ODT is an oral CGRP inhibitor for the acute treatment of migraine and for the preventive treatment of episodic migraine in adults.[12]

142.

11. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Migraine – Calcitonin Gene-Related Peptide Inhibitors – Emgality Prior Authorization Policy
- Emgality® (galcanezumab-gnlm subcutaneous injection – Lilly)

REVIEW DATE: 05/24/2023; selected revision 08/02/2023

OVERVIEW

Emgality, a calcitonin gene-related peptide (CGRP) antagonist, is indicated in adults for the following uses:[1]
- **Episodic cluster headache treatment**.
- **Migraine headache prevention**.

Disease Overview

Migraines have been defined as chronic or episodic. Chronic migraine is described by the International Headache Society as headache occurring on ≥ 15 days/month for > 3 months and has the features of migraine headache on ≥ 8 days/month.[2] Episodic migraine is characterized by headaches that occur < 15 days/month.[4] Episodic migraine is more common than chronic migraine; however, chronic migraine is associated with a markedly greater personal and societal burden.

Cluster headaches are associated with attacks of severe, strictly unilateral pain which is orbital, supraorbital, temporal, or in any combination of these sites, lasting 15 to 180 minutes.[2] The headaches occur from once every other day to eight times a day. Cluster headache is considered among the most severe of the primary headache disorders because of extreme pain, associated autonomic symptoms, and high attack frequency.[5] In addition, a large proportion of patients with cluster headache have chronic cluster headache, which features only brief or no remission periods, and may be particularly refractory to medical therapies.

Guidelines

An updated assessment of the **preventive and acute treatment of migraine** by the **American Headache Society** (AHS) [2018; update 2021] reaffirms previous migraine guidelines.[6,7] Patients with migraine should be considered for preventive treatment in the following situations: when attacks significantly interfere with patients' daily routines despite acute treatment; frequent attacks (≥ 4 monthly headache days); contraindication to, failure, overuse, or adverse events with acute treatments; or patient preference. Before developing a preventive treatment plan, the appropriate use (e.g., drug type, route and timing of administration, frequency) of acute treatments should be initiated and coupled with education and lifestyle modifications. All patients with migraine should be offered a trial of acute treatment. Based on the level of evidence for efficacy and the American Academy of Neurology scheme for classification of evidence, the following oral treatments have established efficacy and should be offered for migraine prevention: antiepileptic drugs (**divalproex sodium, valproate sodium, topiramate** [not for women of childbearing potential without a reliable method of birth control]); beta-blockers (**metoprolol, propranolol, timolol**); and **frovatriptan** (for short-term preventive treatment of menstrual migraine). The following treatments are probably effective and should be considered for migraine prevention: antidepressants (**amitriptyline, venlafaxine**); beta-blockers (**atenolol, nadolol**); and angiotensin receptor blockers (**candesartan**). Additionally, the following treatments are possibly effective and can be considered for migraine prevention: calcium channel blockers (e.g., **verapamil**) and angiotensin converting enzyme inhibitors (e.g., **lisinopril**).[13,14]

Five injectable preventive therapies for migraine are mentioned in the AHS consensus statement: Botox® (onabotulinumtoxinA subcutaneous injection) and four monoclonal antibodies targeting CGRP (Aimovig® [erenumab-aooe subcutaneous injection], Ajovy® [fremanezumab-vfrm subcutaneous injection], Emgality, and Vyepti® [eptinezumab-jjmr intravenous infusion]).[6,7] The update notes that a CGRP inhibitor should only be initiated in patients who are diagnosed with migraine, have ≥ 4 migraine headache days/month, and have intolerance or inadequate response to 6-week trials of at least two traditional oral migraine preventive medications. Additional criteria apply depending on the number and severity of monthly headache days. Clinical judgment may result in an emerging treatment being added to one or more established treatments. If initiating treatment with a CGRP inhibitor in a patient already on a preventive treatment, it is appropriate to add the CGRP inhibitor to the existing regimen and make no other changes until the effectiveness of the CGRP inhibitor is determined since the risk of interactions between traditional oral migraine preventive medications and the CGRP inhibitors is minimal or nonexistent. Making a decision regarding continuation of therapy for a CGRP inhibitor requires a trial of the medication for ≥ 3 months for those administered monthly and ≥ 6 months for those administered quarterly. Treatment should be continued only if benefits can be documented during that time (e.g., reduction in mean monthly headache days of ≥ 50% relative to the pretreatment baseline) or a meaningful improvement on a validated migraine-specific patient-reported outcome measure. Since migraine may improve or remit over time, it is important to re-evaluate the therapeutic response and, if possible, taper or discontinue treatment if patient no longer meets the criteria for offering preventive treatment. However, once control is established, the decision to discontinue or taper treatment should be a shared decision between the patient and clinician.

The **AHS** has published evidence-based guidelines on the **treatment of cluster headache** (2016).[5] The guidelines recommend sumatriptan subcutaneous, zolmitriptan nasal spray, and high flow oxygen for acute treatment. For prophylactic therapy, suboccipital steroid injection has been established as effective for the prophylactic therapy of episodic and chronic cluster headache (Level A). Lithium, verapamil, and melatonin are considered possibly effective for the prophylactic therapy of episodic and chronic cluster headache (Level C). Currently, there is insufficient evidence to make a recommendation for frovatriptan and prednisone (Level U).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Emgality. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Emgality is recommended in those who meet the following criteria:

FDA-Approved Indications

54. Episodic Cluster Headache Treatment. Approve for 6 months if the patient meets the following (A, B, C, and D):
- **39.** Patient is ≥ 18 years of age; AND
- **40.** Patient has between one headache every other day and eight headaches per day; AND
- **41.** Patient has tried at least one standard prophylactic (preventive) pharmacologic therapy for cluster headache; AND

Note: Examples of standard prophylactic (preventive) pharmacologic therapies for cluster headache include lithium, verapamil, melatonin, frovatriptan, prednisone, suboccipital steroid injection, topiramate, and valproate.

42. Patient has had inadequate efficacy or has experienced adverse event(s) severe enough to warrant discontinuation of the standard prophylactic (preventive) pharmacologic therapy, according to the prescriber.

55. Migraine Headache Prevention. Approve for 1 year if the patient meets the following (A, B, C, D, and E):

A) Patient is ≥ 18 years of age; AND

B) Patient has ≥ 4 migraine headache days per month (prior to initiating a migraine-preventive medication); AND

C) Patient has tried at least two standard prophylactic (preventive) pharmacologic therapies, each from a different pharmacologic class; AND

Note: Standard prophylactic (preventive) pharmacologic therapies for migraine include angiotensin receptor blocker, angiotensin converting enzyme inhibitor, anticonvulsant, beta-blocker, calcium channel blocker, tricyclic antidepressant, other antidepressant. A patient who has already tried an oral or injectable calcitonin gene-related peptide (CGRP) inhibitor indicated for the prevention of migraine or Botox (onabotulinumtoxinA injection) for the prevention of migraine is not required to try two standard prophylactic pharmacologic therapies.

D) Patient meets ONE of the following (i, ii, or iii):

i. Patient has had inadequate efficacy to both of those standard prophylactic (preventive) pharmacologic therapies, according to the prescriber; OR

ii. Patient has experienced adverse event(s) severe enough to warrant discontinuation of both of those standard prophylactic (preventive) pharmacologic therapies, according to the prescriber; OR

iii. Patient meets BOTH of the following (a and b):

a) Patient has had inadequate efficacy to one standard prophylactic (preventive) pharmacologic therapy; AND

b) Patient has experienced adverse event(s) severe enough to warrant discontinuation to another standard prophylactic (preventive) pharmacologic therapy, according to the prescriber; AND

E) If the patient is currently taking Emgality, the patient has had a significant clinical benefit from the medication, as determined by the prescriber.

Note: Examples of significant clinical benefit include a reduction in the overall number of migraine days per month or a reduction in number of severe migraine days per month from the time that Emgality was initiated.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Emgality is not recommended in the following situations:

12. Acute Treatment of Migraine. Emgality has not been studied for the acute treatment of migraine.

13. Concurrent use with another calcitonin gene-related peptide (CGRP) inhibitor being prescribed for migraine headache prevention.

Note: CGRP inhibitors that are indicated for migraine headache prevention include Aimovig (erenumab-aooe subcutaneous injection), Ajovy (fremanezumab-vfrm subcutaneous injection), Vyepti (eptinezumab-jjmr intravenous infusion), and Qulipta (atogepant tablets). Ajovy, Aimovig, Emgality, and Vyepti are injectable CGRP inhibitors for migraine prevention and have not been studied for use

in combination with another agent in the same class.[8-10] Qulipta is an oral CGRP inhibitor for the preventive treatment of migraine in adults.[11]

14. **Concurrent use with Nurtec ODT (rimegepant sulfate orally disintegrating tablet) when used as a preventive treatment of migraine.** Nurtec ODT is an oral CGRP inhibitor for the acute treatment of migraine and for the preventive treatment of episodic migraine in adults.[12]

15. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Migraine – Calcitonin Gene-Related Peptide Inhibitors – Vyepti Prior Authorization Policy
- Vyepti® (eptinezumab-jjmr intravenous infusion – Lundbeck)

REVIEW DATE: 05/24/2023; selected revision 08/02/2023

OVERVIEW

Vyepti, a calcitonin gene-related peptide (CGRP) inhibitor, is indicated for the **preventive treatment of migraine** in adults.[1]

Disease Overview

Migraines have been defined as chronic or episodic. Chronic migraine is described by the International Headache Society as headache occurring on ≥ 15 days/month for > 3 months and has the features of migraine headache on ≥ 8 days/month.[2] Episodic migraine is characterized by headaches that occur < 15 days/month.[3,4] Episodic migraine is more common than chronic migraine; however, chronic migraine is associated with a markedly greater personal and societal burden.

Guidelines

An updated assessment of the **preventive and acute treatment of migraine** by the **American Headache Society** (AHS) [2018; update 2021] reaffirms previous migraine guidelines.[5,6] Patients with migraine should be considered for preventive treatment in the following situations: when attacks significantly interfere with patients' daily routines despite acute treatment; frequent attacks (≥ 4 monthly headache days); contraindication to, failure, overuse, or adverse events with acute treatments; or patient preference. Before developing a preventive treatment plan, the appropriate use (e.g., drug type, route and timing of administration, frequency) of acute treatments should be initiated and coupled with education and lifestyle modifications. All patients with migraine should be offered a trial of acute treatment. Based on the level of evidence for efficacy and the American Academy of Neurology scheme for classification of evidence, the following oral treatments have established efficacy and should be offered for migraine prevention: antiepileptic drugs (**divalproex sodium, valproate sodium, topiramate** [not for women of childbearing potential without a reliable method of birth control]); beta-blockers (**metoprolol, propranolol, timolol**); and **frovatriptan** (for short-term preventive treatment of menstrual migraine). The following treatments are probably effective and should be considered for migraine prevention: antidepressants (**amitriptyline, venlafaxine**); beta-blockers (**atenolol, nadolol**); and angiotensin receptor blockers (**candesartan**). Additionally, the following treatments are possibly effective and can be considered for migraine prevention: calcium channel blockers (e.g., **verapamil**) and angiotensin converting enzyme inhibitors (e.g., **lisinopril**).[14,15]

Five injectable preventive therapies for migraine are mentioned in the AHS consensus statement: Botox® (onabotulinumtoxinA intramuscular injection) and four monoclonal antibodies targeting CGRP (Aimovig® [erenumab-aooe subcutaneous injection], Ajovy® [fremanezumab-vfrm subcutaneous injection], Emgality® [galcanezumab-gnlm subcutaneous injection], and Vyepti).[5,6] The update notes that a CGRP inhibitor should only be initiated in patients who are diagnosed with migraine, have ≥ 4 migraine headache days/month, and have intolerance or inadequate response to 6-week trials of at least two traditional oral migraine preventive medications. Additional criteria apply depending on the number and severity of monthly headache days. Clinical judgment may result in an emerging treatment being added to one or more established treatments. If initiating treatment with a CGRP inhibitor in a patient already on a preventive treatment, it is appropriate to add the CGRP inhibitor to the existing regimen. When doing so, make no

other changes until the effectiveness of the CGRP inhibitor is determined since the risk of interactions between traditional oral migraine preventive medications and the CGRP inhibitors is minimal or nonexistent. Making a decision regarding continuation of therapy for a CGRP inhibitor requires a trial of the medication for ≥ 3 months for those administered monthly and ≥ 6 months for those administered quarterly. Treatment should be continued only if benefits can be documented during that time (e.g., reduction in mean monthly headache days of ≥ 50% relative to the pretreatment baseline) or a meaningful improvement on a validated migraine-specific patient-reported outcome measure. Since migraine may improve or remit over time, it is important to re-evaluate the therapeutic response and, if possible, taper or discontinue treatment if patient no longer meets the criteria for offering preventive treatment. However, once control is established, the decision to discontinue or taper treatment should be a shared decision between the patient and clinician.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vyepti. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vyepti is recommended in those who meet the following criteria:

FDA-Approved Indication

56. Migraine Headache Prevention. Approve Vyepti for 1 year if the patient meets the following (A, B, C, D, and E):

43. Patient is ≥ 18 years of age; AND

44. Patient has ≥ 4 migraine headache days per month (prior to initiating a migraine-preventive medication); AND

45. Patient has tried at least two standard prophylactic (preventive) pharmacologic therapies, each from a different pharmacologic class; AND

Note: Standard prophylactic (preventive) pharmacologic therapies include angiotensin receptor blocker, angiotensin converting enzyme inhibitor, anticonvulsant, β-blocker, calcium channel blocker, tricyclic antidepressant, other antidepressant. A patient who has already tried an oral or injectable calcitonin gene-related peptide (CGRP) inhibitor indicated for the prevention of migraine or Botox (onabotulinumtoxinA injection) for the prevention of migraine is not required to try two standard prophylactic pharmacologic therapies.

46. Patient meets ONE of the following (i, ii, or iii):

i. Patient has had inadequate efficacy to both of those standard prophylactic (preventive) pharmacologic therapies, according to the prescriber; OR

ii. Patient has experienced adverse event(s) severe enough to warrant discontinuation of both of those standard prophylactic (preventive) pharmacologic therapies, according to the prescriber; OR

iii. Patient meets BOTH of the following (a and b):

a) Patient has had inadequate efficacy to one standard prophylactic (preventive) pharmacologic therapy; AND

b) Patient has experienced adverse event(s) severe enough to warrant discontinuation of another standard prophylactic (preventive) pharmacologic therapy, according to the prescriber; AND

47. If the patient is currently taking Vyepti, the patient has had a significant clinical benefit from the medication as determined by the prescriber.
Note: Examples of significant clinical benefit include a reduction in the overall number of migraine days per month or a reduction in number of severe migraine days per month from the time that Vyepti was initiated.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vyepti is not recommended in the following situations:

227. Acute Treatment of Migraine. Clinical data are currently lacking for the use of Vyepti in the acute treatment of migraine.

228. Cluster Headache, Treatment or Prevention. Clinical data are currently lacking for the use of Vyepti in patients with cluster headache. The pivotal trials of Vyepti excluded patients with this condition.[7,8]

229. Concurrent use with another calcitonin gene-related peptide (CGRP) inhibitor being prescribed for migraine headache prevention.
Note: CGRP inhibitors that are indicated for migraine headache prevention include Aimovig (erenumab-aooe subcutaneous injection), Ajovy (fremanezumab-vfrm subcutaneous injection), Emgality (galcanezumab-gnlm subcutaneous injection), and Qulipta (atogepant tablets). Aimovig, Ajovy, Emgality, and Vyepti are CGRP inhibitors for migraine prevention and have not been studied for use in combination with another agent in the same class.[9-11] Qulipta is an oral CGRP inhibitor for the preventive treatment of migraine in adults.[12]

230. Concurrent use with Nurtec ODT (rimegepant sulfate orally disintegrating tablet) when used as a preventive treatment of migraine. Nurtec ODT is an oral CGRP inhibitor for the acute treatment of migraine and for the preventive treatment of episodic migraine in adults.[13]

231. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Migraine – Elyxyb Prior Authorization Policy
- Elyxyb™ (celecoxib oral solution – BioDelivery Sciences)

REVIEW DATE: 03/22/2023

OVERVIEW

Elyxyb, a nonsteroidal anti-inflammatory drug, is indicated for the **acute treatment of migraine with or without aura** in adults [1] Limitations of Use: Elyxyb is not indicated for the preventive treatment of migraine.

Disease Overview

Migraine is a common, ongoing condition marked by paroxysmal, unilateral attacks of moderate to severe throbbing headache which are aggravated by routine physical activity (e.g., walking or climbing stairs) and associated with nausea, vomiting, and/or photophobia and phonophobia.[2] Migraines have been defined as chronic or episodic. Chronic migraine is described by the International Headache Society as headache occurring on ≥ 15 days/month for more than 3 months, which has the features of migraine headache on ≥ 8 days/month. Episodic migraine is characterized by headaches that occur < 15 days/month.[3]

Guidelines

Triptans (e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) are considered the gold standard for acute treatment of moderate to severe migraine headaches or mild to moderate migraine headaches that respond poorly to over-the-counter analgesics. An assessment of the preventive and acute treatment of migraine by the American Headache Society (2018; updated 2021) reaffirms previous migraine guidelines.[4,5] Nonsteroidal anti-inflammatory drugs (NSAIDs) as a class are mentioned as an option for acute treatment of mild to moderate migraine attacks; celecoxib is not specifically addressed. The potential for cardiovascular and gastrointestinal adverse events with NSAID use is noted. Other treatment options in the mild to moderate setting include nonopioid analgesics, acetaminophen, or caffeinated analgesic combinations. For moderate to severe attacks or attacks which respond poorly to NSAIDs or caffeinated combinations, the update lists the triptans, dihydroergotamine, the oral gepants (Nurtec® ODT [rimegepant orally disintegrating tablets,] and Ubrelvy® [ubrogepant tablets]), and Reyvow™ (lasmiditan tablet) as effective treatments. The recommendation remains that clinicians must consider medication efficacy and potential medication-related adverse events when prescribing acute medications for migraine.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Elyxyb. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Elyxyb is recommended in those who meet the following criteria:

FDA-Approved Indication

155. Migraine, Acute Treatment. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient is ≥ 18 years of age; AND

B) Patient meets ONE of the following (i or ii):

i. Patient has tried at least one triptan therapy; OR

ii. Patient has a contraindication to triptan(s) according to the prescriber.
Note: Examples of contraindications to triptans include a history of coronary artery disease; cardiac accessory conduction pathway disorders; of stroke, transient ischemic attack, or hemiplegic or basilar migraine; peripheral vascular disease; ischemic bowel disease; uncontrolled hypertension; or severe hepatic impairment.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Elyxyb is not recommended in the following situations:

232. Management of Acute Pain Unrelated to Migraine Headache. Celecoxib is also available as a capsule (Celebrex®, generic).[6] Celecoxib capsules are indicated for the management of the signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis in adults and juvenile rheumatoid arthritis in patients ≥ 2 years of age; acute pain in adults; and primary dysmenorrhea in adults. For patients who have difficulty swallowing capsules, the contents of a celecoxib capsule can be added to applesauce. There are no published studies with Elyxyb in acute pain.

233. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Migraine – Nurtec ODT Prior Authorization Policy
- Nurtec® ODT (rimegepant sulfate orally disintegrating tablets – Biohaven)

REVIEW DATE: 02/15/2023; selected revision 08/02/2023

OVERVIEW

Nurtec ODT, a calcitonin gene-related peptide (CGRP) receptor antagonist, is indicated in adults for the following uses:[1]

- **Acute treatment of migraine** with or without aura.
- **Preventive treatment of episodic migraine**.

Disease Overview

Migraine is a common, ongoing condition marked by paroxysmal, unilateral attacks of moderate to severe throbbing headache which is aggravated by routine physical activity (e.g., walking or climbing stairs) and associated with nausea, vomiting, and/or photophobia and phonophobia.[2] Migraines have been defined as chronic or episodic. Chronic migraine is described by the International Headache Society as headache occurring on ≥ 15 days/month for more than 3 months, which has the features of migraine headache on ≥ 8 days/month. Episodic migraine is characterized by headaches that occur < 15 days/month.

Guidelines

Triptans (e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) are considered the gold standard for acute treatment of moderate to severe migraine headaches or mild to moderate migraine headaches that respond poorly to over-the-counter analgesics.[2] An assessment of the preventive and acute treatment of migraine by the American Headache Society (2018; updated 2021) reaffirms previous migraine guidelines.[3,4] Nurtec ODT is not addressed for its preventive treatment of episodic migraine indication in the guideline. The update lists the triptans, dihydroergotamine, the oral gepants (Nurtec ODT and Ubrelvy® [ubrogepant tablets]), and Reyvow® (lasmiditan tablets) as effective treatments for moderate or severe acute migraine attacks and mild to moderate attacks that respond poorly to nonsteroidal anti-inflammatory drugs, non-opioid analgesics, acetaminophen, or caffeinated combinations (e.g., aspirin + acetaminophen + caffeine).

Patients with migraine should be considered for preventive treatment when attacks significantly interfere with patients' daily routines despite acute treatment; frequent attacks (≥ 4 monthly headache days); contraindication to, failure, overuse, or adverse events with acute treatments; or patient preference.[3,4] Before developing a preventive treatment plan, the appropriate use of acute treatments should be initiated and coupled with education and lifestyle modifications. All patients with migraine should be offered a trial of acute treatment. Based on the level of evidence for efficacy and the American Academy of Neurology scheme for classification of evidence, the following oral medications have established efficacy and should be offered for migraine prevention: antiepileptic drugs (**divalproex sodium, valproate sodium, topiramate** [not for women of childbearing potential without a reliable method of birth control]); beta-blockers (**metoprolol, propranolol, timolol**); and **frovatriptan** (for short-term preventive treatment of menstrual migraine). The following treatments are probably effective and should be considered for migraine prevention: antidepressants (**amitriptyline, venlafaxine**); beta-blockers (**atenolol, nadolol**); and angiotensin receptor blockers (**candesartan**). Additionally, the following treatments are possibly effective and can be considered for migraine prevention: calcium channel blockers (e.g., **verapamil**) and angiotensin converting enzyme inhibitors (e.g., **lisinopril**).[10,11]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Nurtec ODT. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Nurtec ODT is recommended in those who meet one of the following criteria:

FDA-Approved Indications

156. Migraine, Acute Treatment. Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following (i or ii):
  - **i.** Patient has tried at least one triptan therapy; OR
  - **ii.** Patient has a contraindication to triptan(s) according to the prescriber.
    Note: Examples of contraindications to triptans include a history of coronary artery disease; cardiac accessory conduction pathway disorders; of stroke, transient ischemic attack, or hemiplegic or basilar migraine; peripheral vascular disease; ischemic bowel disease; uncontrolled hypertension; or severe hepatic impairment.

57. Preventive Treatment of Episodic Migraine. Approve for 1 year if the patient meets the following (A, B, C, D, and E):
- **48.** Patient is ≥ 18 years of age; AND
- **49.** Patient has ≥ 4 and < 15 migraine headache days per month (prior to initiating a migraine-preventive medication); AND
- **50.** Patient has tried at least two standard prophylactic (preventive) pharmacologic therapies, each from a different pharmacologic class; AND
  Note: Standard prophylactic (preventive) pharmacologic therapies include angiotensin receptor blocker, anticonvulsant, beta-blocker, tricyclic antidepressant, other antidepressant. A patient who has already tried an oral or injectable calcitonin gene-related peptide (CGRP) inhibitor indicated for the prevention of migraine or Botox (onabotulinumtoxinA injection) for the prevention of migraine is not required to try two standard prophylactic pharmacologic therapies.
- **51.** Patient meets ONE of the following (i, ii, or iii):
  - **i.** Patient has had inadequate efficacy to both of those standard prophylactic (preventive) pharmacologic therapies, according to the prescriber; OR
  - **ii.** Patient has experienced adverse event(s) severe enough to warrant discontinuation of both of those standard prophylactic (preventive) pharmacologic therapies, according to the prescriber; OR
  - **iii.** Patient has had inadequate efficacy to one standard prophylactic (preventive) pharmacologic therapy and has experienced adverse event(s) severe enough to warrant discontinuation of another standard prophylactic (preventive) pharmacologic therapy, according to the prescriber; AND
- **52.** If the patient is currently taking Nurtec ODT, patient has had a significant clinical benefit from the medication as determined by the prescriber.
  Note: Examples of significant clinical benefit include a reduction in the overall number of migraine days per month or a reduction in number of severe migraine days per month from the time that Nurtec ODT was initiated.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nurtec ODT is not recommended in the following situations:

234. Concurrent use with another calcitonin gene-related peptide (CGRP) inhibitor being prescribed for migraine headache prevention if Nurtec ODT is being taken for the preventive treatment of episodic migraine.

Note: Examples of CGRP inhibitors that are indicated for migraine headache prevention include Aimovig (erenumab-aooe subcutaneous injection), Ajovy (fremanezumab-vfrm subcutaneous injection), Emgality (galcanezumab-gnlm subcutaneous injection), Vyepti (eptinezumab-jjmr intravenous infusion), Nurtec ODT (rimegepant sulfate orally disintegrating tablets), and Qulipta (atogepant tablets). Aimovig, Ajovy, Emgality, and Vyepti are injectable CGRP inhibitors for migraine prevention and have not been studied for use in combination with another agent in the same class.[5-8] Qulipta is an oral CGRP inhibitor for the preventive treatment of episodic migraine in adults.[9] The clinical trial of Nurtec ODT for the preventive treatment of episodic migraine did not allow the use of a concomitant medication that acts on the CGRP pathway.[1]

235. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

717. Nurtec® ODT [prescribing information]. New Haven, CT: Biohaven; April 2022.
718. MacGregor EA. In the clinic. Migraine. *Ann Intern Med*. 2017;166(7):ITC49-ITC64.
719. American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019;59:1-18.
720. Ailani J, Burch RC, Robbins MS, on behalf of the Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. *Headache*. 2021;61(7):1021-1039.
721. Aimovig® subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; October 2022.
722. Ajovy® subcutaneous injection [prescribing information]. North Wales, PA: Teva; September 2021.
723. Emgality® subcutaneous injection [prescribing information]. Indianapolis, IN: Lilly; May 2022.
724. Vyepti® intravenous infusion [prescribing information]. Bothell, WA: Lundbeck; October 2022.
725. Qulipta™ tablets [prescribing information]. Madison, NJ: AbbVie; September 2021.
726. Micromedex. Merative LP. Available at: https://www.micromedexsolutions.com/. Accessed on August 7, 2023. Search terms: lisinopril, verapamil.
727. Clinical Pharmacology. ClinicalKey. Available at: https://www.clinicalkey.com/pharmacology/. Accessed on August 7, 2023. Search terms: lisinopril, verapamil.

PRIOR AUTHORIZATION POLICY

POLICY: Migraine – Qulipta Prior Authorization Policy
- Qulipta™ (atogepant tablets – AbbVie)

REVIEW DATE: 02/15/2023; selected revision 05/03/2023 and 08/02/2023

OVERVIEW

Qulipta, a calcitonin gene-related peptide (CGRP) receptor antagonist, is indicated for the **preventive treatment of migraine** in adults.[1]

Disease Overview

Migraine is a common, ongoing condition marked by paroxysmal, unilateral attacks of moderate to severe throbbing headache.[2] Migraines are aggravated by routine physical activity (e.g., walking or climbing stairs) and associated with nausea, vomiting, and/or photophobia and phonophobia. Migraines have been defined as chronic or episodic. Chronic migraine is described by the International Headache Society as headache occurring on ≥ 15 days/month for more than 3 months, which has the features of migraine headache on ≥ 8 days/month. Episodic migraine is characterized by headaches that occur < 15 days/month.

Guidelines

An assessment of the preventive and acute treatment of migraine by the American Headache Society (2018; updated 2021) reaffirms previous migraine guidelines.[3,4] Patients with migraine should be considered for preventive treatment when attacks significantly interfere with patients' daily routines despite acute treatment; frequent attacks (≥ 4 monthly headache days); contraindication to, failure, overuse, or adverse events with acute treatments; or patient preference. Before developing a preventive treatment plan, the appropriate use (e.g., drug type, route and timing of administration, frequency) of acute treatments should be initiated and coupled with education and lifestyle modifications. Based on the level of evidence for efficacy and the American Academy of Neurology scheme for classification of evidence, the following oral treatments have established efficacy and should be offered for migraine prevention: antiepileptic drugs (**divalproex sodium, valproate sodium, topiramate** [not for women of childbearing potential without a reliable method of birth control]); beta-blockers (**metoprolol, propranolol, timolol**); and **frovatriptan** (for short-term preventive treatment of menstrual migraine). The following treatments are probably effective and should be considered for migraine prevention: antidepressants (**amitriptyline, venlafaxine**); beta-blockers (**atenolol, nadolol**); and angiotensin receptor blockers (**candesartan**). Additionally, the following treatments are possibly effective and can be considered for migraine prevention: calcium channel blockers (e.g., **verapamil**) and angiotensin converting enzyme inhibitors (e.g., **lisinopril**).[10,11]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Qulipta. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Qulipta is recommended in those who meet the following criteria:

FDA-Approved Indication

58. Migraine Headache Prevention. Approve for 1 year if the patient meets the following (A, B, C, D, and E):

53. Patient is ≥ 18 years of age; AND

54. Patient has ≥ 4 migraine headache days per month (prior to initiating a migraine-preventive medication); AND

55. Patient has tried at least two standard prophylactic (preventive) pharmacologic therapies, each from a different pharmacologic class; AND

Note: Standard prophylactic (preventive) pharmacologic therapies include angiotensin receptor blocker, anticonvulsant, beta-blocker, tricyclic antidepressant, other antidepressant. A patient who has already tried an oral or injectable calcitonin gene-related peptide (CGRP) inhibitor indicated for the prevention of migraine or Botox (onabotulinumtoxinA injection) for the prevention of migraine is not required to try two standard prophylactic pharmacologic therapies.

56. Patient meets ONE of the following (i, ii, or iii):

i. Patient has had inadequate efficacy to both of those standard prophylactic (preventive) pharmacologic therapies, according to the prescriber; OR

ii. Patient has experienced adverse event(s) severe enough to warrant discontinuation of both of those standard prophylactic (preventive) pharmacologic therapies, according to the prescriber; OR

iii. Patient has had inadequate efficacy to one standard prophylactic (preventive) pharmacologic therapy and has experienced adverse event(s) severe enough to warrant discontinuation of another standard prophylactic (preventive) pharmacologic therapy, according to the prescriber; AND

57. If the patient is currently taking Qulipta, patient has had a significant clinical benefit from the medication as determined by the prescriber.

Note: Examples of significant clinical benefit include a reduction in the overall number of migraine days per month or a reduction in number of severe migraine days per month from the time that Qulipta was initiated.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Qulipta is not recommended in the following situations:

236. Concurrent Use with Another Calcitonin Gene-Related Peptide (CGRP) Inhibitor Being Prescribed for Migraine Headache Prevention.

Note: CGRP inhibitors that are indicated for migraine headache prevention include Aimovig (erenumab-aooe subcutaneous injection), Ajovy (fremanezumab-vfrm subcutaneous injection), Emgality (galcanezumab-gnlm subcutaneous injection), Vyepti (eptinezumab-jjmr intravenous infusion), Nurtec ODT (rimegepant sulfate orally disintegrating tablets), and Qulipta (atogepant tablets). Aimovig, Ajovy, Emgality, and Vyepti are injectable CGRP inhibitors for migraine prevention and have not been studied for use in combination with another agent in the same class.[5-8] Nurtec ODT is an oral CGRP inhibitor indicated for the acute treatment of migraine and for preventive treatment of episodic migraine.[9] Clinical trials of Nurtec ODT for the prevention of episodic migraine did not permit the use of a concomitant medication that acts on the CGRP pathway.

237. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

728. Qulipta™ tablets [prescribing information]. Madison, NJ: AbbVie; March 2023.
729. MacGregor EA. In the clinic. Migraine. *Ann Intern Med*. 2017;166(7):ITC49-ITC64.
730. American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019;59:1-18.
731. Ailani J, Burch RC, Robbins MS, on behalf of the Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. *Headache*. 2021;61(7):1021-1039.
732. Aimovig® subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; October 2022.
733. Ajovy® subcutaneous injection [prescribing information]. North Wales, PA: Teva; September 2021.
734. Emgality® subcutaneous injection [prescribing information]. Indianapolis, IN: Lilly; May 2022.
735. Vyepti® intravenous injection [prescribing information]. Bothell, WA: Lundbeck; October 2022.
736. Nurtec® ODT orally disintegrating tablets [prescribing information]. New Haven, CT: Biohaven; April 2022.
737. Micromedex. Merative LP. Available at: https://www.micromedexsolutions.com/. Accessed on August 7, 2023. Search terms: lisinopril, verapamil.
738. Clinical Pharmacology. ClinicalKey. Available at: https://www.clinicalkey.com/pharmacology/ Accessed on August 7, 2023. Search terms: lisinopril, verapamil.

PRIOR AUTHORIZATION POLICY

POLICY: Migraine – Reyvow Prior Authorization Policy
- Reyvow® (lasmiditan tablets – Lilly)

REVIEW DATE: 07/26/2023

OVERVIEW

Reyvow, a serotonin subtype 1F receptor agonist, is indicated for the **acute treatment of migraine** with or without aura in adults.[1] Limitations of Use: Reyvow is not indicated for the preventive treatment of migraine.

Disease Overview

Migraine is a common, ongoing condition marked by paroxysmal, unilateral attacks of moderate to severe throbbing headache which are aggravated by routine physical activity (e.g., walking or climbing stairs) and associated with nausea, vomiting, and/or photophobia and phonophobia.[2] Migraines have been defined as chronic or episodic. Chronic migraine is described by the International Headache Society as headache occurring on ≥ 15 days/month for more than 3 months, which has the features of migraine headache on ≥ 8 days/month. Episodic migraine is characterized by headaches that occur < 15 days/month.[3]

Guidelines

Triptans (e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) are considered the gold standard for acute treatment of moderate to severe migraine headaches or mild to moderate migraine headaches that respond poorly to over-the-counter analgesics. An assessment of the preventive and acute treatment of migraine by the American Headache Society (2018; updated 2021) reaffirms previous migraine guidelines.[4,5] The update lists the triptans, dihydroergotamine, the oral gepants (Nurtec® ODT [rimegepant orally disintegrating tablets,] and Ubrelvy® [ubrogepant tablets]), and Reyvow as effective treatments for moderate or severe acute migraine attacks and mild to moderate attacks that respond poorly to nonsteroidal anti-inflammatory drugs, non-opioid analgesics, acetaminophen, or caffeinated combinations (e.g., aspirin + acetaminophen + caffeine). The recommendation remains that clinicians must consider medication efficacy and potential medication-related adverse events when prescribing acute medications for migraine.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Reyvow. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Reyvow is recommended in those who meet the following criteria:

FDA-Approved Indication

157. Migraine, Acute Treatment. Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following (i or ii):
  - **i.** Patient has tried at least one triptan therapy; OR
  - **ii.** Patient has a contraindication to triptan(s) according to the prescriber.
    Note: Examples of contraindications to triptans include a history of coronary artery disease; cardiac accessory conduction pathway disorders; of stroke, transient ischemic attack, or hemiplegic or basilar migraine; peripheral vascular disease; ischemic bowel disease; uncontrolled hypertension; or severe hepatic impairment.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Reyvow is not recommended in the following situations:

238. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

739. Reyvow® tablets [prescribing information]. Indianapolis, IN: Lilly; September 2022.
740. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition. *Cephalalgia*. 2018;38(1):1-211.
741. Lipton RB, Silberstein SD. Episodic and chronic migraine headache: breaking down barriers to optimal treatment and prevention. *Headache*. 2015;52:103-122.
742. American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019;59:1-18.
743. Ailani J, Burch RC, Robbins MS, on behalf of the Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. *Headache*. 2021;61(7):1021-1039.

PRIOR AUTHORIZATION POLICY

POLICY: Migraine – Ubrelvy Prior Authorization Policy
- Ubrelvy® (ubrogepant tablets – Allergan)

REVIEW DATE: 02/15/2023

OVERVIEW

Ubrelvy, a calcitonin gene-related peptide receptor antagonist, is indicated for the **acute treatment of migraine headache** with or without aura in adults.[1] Limitations of Use: Ubrelvy is not indicated for the preventive treatment of migraine.

Disease Overview

Migraine is a common, ongoing condition marked by paroxysmal, unilateral attacks of moderate to severe throbbing headache which are aggravated by routine physical activity (e.g., walking or climbing stairs) and associated with nausea, vomiting, and/or photophobia and phonophobia.[2] Migraines have been defined as chronic or episodic. Chronic migraine is described by the International Headache Society as headache occurring on ≥ 15 days/month for more than 3 months, which has the features of migraine headache on ≥ 8 days/month. Episodic migraine is characterized by headaches that occur < 15 days/month.[3]

Guidelines

Triptans (e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) are considered the gold standard for acute treatment of moderate to severe migraine headaches or mild to moderate migraine headaches that respond poorly to over-the-counter analgesics. An assessment of the preventive and acute treatment of migraine by the American Headache Society (2018; updated 2021) reaffirms previous migraine guidelines.[4,5] The update lists the triptans, dihydroergotamine, the oral gepants (Nurtec® ODT [rimegepant orally disintegrating tablets,] and Ubrelvy® [ubrogepant tablets]), and Reyvow® (lasmiditan tablets) as effective treatments for moderate or severe acute migraine attacks and mild to moderate attacks that respond poorly to nonsteroidal anti-inflammatory drugs, non-opioid analgesics, acetaminophen, or caffeinated combinations (e.g., aspirin + acetaminophen + caffeine). The recommendation remains that clinicians must consider medication efficacy and potential medication-related adverse events when prescribing acute medications for migraine.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ubrelvy. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ubrelvy is recommended in those who meet the following criteria:

FDA-Approved Indication

158. Migraine, Acute Treatment. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient is ≥ 18 years of age; AND

B) Patient meets ONE of the following (i or ii):

i. Patient has tried at least one triptan therapy; OR

ii. Patient has a contraindication to triptan(s) according to the prescriber.
Note: Examples of contraindications to triptans include a history of coronary artery disease; cardiac accessory conduction pathway disorders; of stroke, transient ischemic attack, or hemiplegic or basilar migraine; peripheral vascular disease; ischemic bowel disease; uncontrolled hypertension; or severe hepatic impairment.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ubrelvy is not recommended in the following situations:

239. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

744. Ubrelvy® tablets [prescribing information]. Madison, NJ: Allergan; March 2021.
745. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition. *Cephalalgia*. 2018;38(1):1-211.
746. Lipton RB, Silberstein SD. Episodic and chronic migraine headache: breaking down barriers to optimal treatment and prevention. *Headache*. 2015;52:103-122.
747. American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019;59:1-18.
748. Ailani J, Burch RC, Robbins MS, on behalf of the Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. *Headache*. 2021;61(7):1021-1039.

PRIOR AUTHORIZATION POLICY

POLICY: Migraine – Zavzpret Prior Authorization Policy
- Zavzpret™ (zavegepant nasal spray – Pfizer)

REVIEW DATE: 04/26/2023

OVERVIEW

Zavzpret, a calcitonin gene-related peptide receptor antagonist, is indicated for the **acute treatment of migraine headache** with or without aura in adults.[1] Limitations of Use: Zavzpret is not indicated for the preventive treatment of migraine.

Disease Overview

Migraine is a common, ongoing condition marked by paroxysmal, unilateral attacks of moderate to severe throbbing headache which are aggravated by routine physical activity (e.g., walking or climbing stairs) and associated with nausea, vomiting, and/or photophobia and phonophobia.[2] Migraines have been defined as chronic or episodic. Chronic migraine is described by the International Headache Society as headache occurring on ≥ 15 days/month for more than 3 months, which has the features of migraine headache on ≥ 8 days/month. Episodic migraine is characterized by headaches that occur < 15 days/month.[3]

Guidelines

Zavzpret has not been included in guidelines. Triptans (e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) are considered the gold standard for acute treatment of moderate to severe migraine headaches or mild to moderate migraine headaches that respond poorly to over-the-counter analgesics. An assessment of the preventive and acute treatment of migraine by the American Headache Society (2018; updated 2021) reaffirms previous migraine guidelines.[4,5] The update lists the triptans, dihydroergotamine, the oral gepants (Nurtec® ODT [rimegepant orally disintegrating tablets,] and Ubrelvy® [ubrogepant tablets]), and Reyvow® (lasmiditan tablets) as effective treatments for moderate or severe acute migraine attacks and mild to moderate attacks that respond poorly to nonsteroidal anti-inflammatory drugs, non-opioid analgesics, acetaminophen, or caffeinated combinations (e.g., aspirin + acetaminophen + caffeine). The recommendation remains that clinicians must consider medication efficacy and potential medication-related adverse events when prescribing acute medications for migraine.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zavzpret. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zavzpret is recommended in those who meet the following criteria:

FDA-Approved Indication

159. Migraine, Acute Treatment. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient is ≥ 18 years of age; AND

B) Patient meets ONE of the following (i or ii):

i. Patient has tried at least one triptan therapy; OR

ii. Patient has a contraindication to triptan(s) according to the prescriber.
Note: Examples of contraindications to triptans include a history of coronary artery disease; cardiac accessory conduction pathway disorders; of stroke, transient ischemic attack, or hemiplegic or basilar migraine; peripheral vascular disease; ischemic bowel disease; uncontrolled hypertension; or severe hepatic impairment.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zavzpret is not recommended in the following situations:

240. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

749. Zavzpret™ tablets [prescribing information]. New York, NY: Pfizer; March 2023.
750. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition. *Cephalalgia*. 2018;38(1):1-211.
751. Lipton RB, Silberstein SD. Episodic and chronic migraine headache: breaking down barriers to optimal treatment and prevention. *Headache*. 2015;52:103-122.
752. American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019;59:1-18.
753. Ailani J, Burch RC, Robbins MS, on behalf of the Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. *Headache*. 2021;61(7):1021-1039.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Avonex Prior Authorization Policy
- Avonex® (interferon beta-1a intramuscular injection – Biogen)

REVIEW DATE: 11/08/2023

OVERVIEW

Avonex is indicated for the treatment of patients with relapsing forms of **multiple sclerosis** (MS) to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in adults.[1]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[2-4] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

IN SEPTEMBER 2019, A CONSENSUS PAPER WAS UPDATED BY THE MS COALITION THAT DISCUSSES THE USE OF DISEASE-MODIFYING THERAPIES IN MS.[2] MANY OPTIONS FROM VARIOUS DISEASE CLASSES, INVOLVING DIFFERENT MECHANISMS OF ACTION AND MODES OF ADMINISTRATION, HAVE SHOWN BENEFITS IN PATIENTS WITH MS.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Avonex. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Avonex as well as the monitoring required for adverse events and long-term efficacy, approval requires Avonex to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Avonex is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Multiple Sclerosis.** Approve for the duration noted below if the patient meets one of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets the following (i and ii):
     - **i.** Patient has a relapsing form of multiple sclerosis; AND
       Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
     - **ii.** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.
   - **B)** Patient is Currently Receiving Avonex for ≥ 1 Year. Approve for 1 year if the patient meets the following (i, ii, and iii):
   - **i.** Patient has a relapsing form of multiple sclerosis; AND
     Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
   - **ii.** Patient meets one of the following (a or b):
     - **a)** Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
       Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability State Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item MS Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.
     - **b)** Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND
   - **iii.** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Avonex is not recommended in the following situations:

21. **Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.** These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

22. **Non-Relapsing Forms of Multiple Sclerosis.** The efficacy of Avonex has not been established in patients with non-relapsing forms of multiple sclerosis.[1]
    Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

23. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

13. Avonex® intramuscular injection [prescribing information]. Cambridge, MA: Biogen; July 2023.
14. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. September 2019. Available at: http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed on November 4, 2023.
15. McGinley MP, Goldschmidt C, Rae-Grant AD. Diagnosis and treatment of multiple sclerosis. A review. *JAMA*. 2021;325(8):765-779.
16. No authors listed. Drugs for multiple sclerosis. *Med Lett Drugs Ther*. 2021;63(1620):42-48.
17. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
18. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.

APPENDIX

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Bafiertam Prior Authorization Policy
- Bafiertam® (monomethyl fumarate delayed-release capsules – Banner Life Sciences)

REVIEW DATE: 11/08/2023

OVERVIEW

Bafiertam is indicated for the treatment of relapsing forms of **multiple sclerosis** (MS) to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive MS in adults.[1]

Disease Overview

44. MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[2-4] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

IN SEPTEMBER 2019, A CONSENSUS PAPER WAS UPDATED BY THE MS COALITION THAT DISCUSSES THE USE OF DISEASE-MODIFYING THERAPIES IN MS.[2] MANY OPTIONS FROM VARIOUS DISEASE CLASSES, INVOLVING DIFFERENT MECHANISMS OF ACTION AND MODES OF ADMINISTRATION, HAVE SHOWN BENEFITS IN PATIENTS WITH MS.

Safety

Progressive multifocal leukoencephalopathy has occurred in patients with MS treated with Tecfidera® (dimethyl fumarate delayed-release capsules), which is the prodrug of Bafiertam.[1]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Bafiertam. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Bafiertam as well as the monitoring required for adverse events and efficacy, approval requires Bafiertam to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Bafiertam is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Multiple Sclerosis.** Approve for the duration noted below if the patient meets one of the following (A or B):

A) Initial Therapy. Approve for 1 year if the patient meets the following (i and ii):

i. Patient has a relapsing form of multiple sclerosis; AND
Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

ii. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR

B) Patient is Currently Receiving Bafiertam for ≥ 1 Year. Approve for 1 year if the patient meets the following (i, ii, and iii):

i. Patient has a relapsing form of multiple sclerosis; AND
Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

ii. Patient meets one of the following (a or b):

a) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability State Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item MS Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.

b) Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND

iii. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Bafiertam is not recommended in the following situations:

70. Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis. These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

71. Non-Relapsing Forms of Multiple Sclerosis. The efficacy of Bafiertam has not been established in patients with non-relapsing forms of multiple sclerosis.[1]
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

72. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

186. Bafiertam® delayed-release capsules [prescribing information]. High Point, NC: Banner Life Sciences; January 2023.
187. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. Updated September 2019. Available at: http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed on November 4, 2023.
188. McGinley MP, Goldschmidt C, Rae-Grant AD. Diagnosis and treatment of multiple sclerosis. A review. *JAMA*. 2021;325(8):765-779.
189. No authors listed. Drugs for multiple sclerosis. *Med Lett Drugs Ther*. 2021;63(1620):42-48.
190. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
191. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.

APPENDIX

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Betaseron/Extavia Prior Authorization Policy
- Betaseron® (interferon beta-1b subcutaneous injection – Bayer)
- Extavia® (interferon beta-1b subcutaneous injection – Novartis)

REVIEW DATE: 11/08/2023

OVERVIEW

Betaseron and Extavia are indicated for the treatment of relapsing forms of **multiple sclerosis** (MS) to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults.[1,2] Extavia and Betaseron are essentially the same formulation of interferon beta-1b. The only difference is that Extavia is supplied with a 27 gauge needle compared to a 30 gauge needle that is given with Betaseron.

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[3-5] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders.[3-5] Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[6] as well as in 2017.[7] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[3-7] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

IN SEPTEMBER 2019, A CONSENSUS PAPER WAS UPDATED BY THE MS COALITION THAT DISCUSSES THE USE OF DISEASE-MODIFYING THERAPIES IN MS.[3] MANY OPTIONS FROM VARIOUS DISEASE CLASSES, INVOLVING DIFFERENT MECHANISMS OF ACTION AND MODES OF ADMINISTRATION, HAVE SHOWN BENEFITS IN PATIENTS WITH MS.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Betaseron and Extavia. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Betaseron/Extavia as well as the monitoring required for adverse events and long-term efficacy, approval requires Betaseron and Extavia to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Betaseron/Extavia is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Multiple Sclerosis.** Approve for the duration noted below if the patient meets one of the following (A or B):
   A) Initial Therapy. Approve for 1 year if the patient meets the following (i and ii):
   iii. Patient has a relapsing form of multiple sclerosis; AND
   Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
   iv. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR
   B) Patient is Currently Receiving Betaseron or Extavia for ≥ 1 Year. Approve for 1 year if the patient meets the following (i, ii, and iii):
   iv. Patient has a relapsing form of multiple sclerosis; AND
   Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
   v. Patient meets one of the following (a or b):
   c) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
   Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability State Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item MS Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.
   d) Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND
   vi. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Betaseron/Extavia is not recommended in the following situations:

~~24.~~ **Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.** These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

25. Non-Relapsing Forms of Multiple Sclerosis. The efficacy of Betaseron/Extavia have not been established in patients with non-relapsing forms of multiple sclerosis.[1]
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

26. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

19. Betaseron® subcutaneous injection [prescribing information]. Whippany, NJ: Bayer; July 2023.
20. Extavia® subcutaneous injection [prescribing information]. East Hanover, NJ: Novartis; July 2023.
21. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. September 2019. Available at: http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed on November 4, 2023.
22. McGinley MP, Goldschmidt C, Rae-Grant AD. Diagnosis and treatment of multiple sclerosis. A review. *JAMA*. 2021;325(8):765-779.
23. No authors listed. Drugs for multiple sclerosis. *Med Lett Drugs Ther*. 2021;63(1620):42-48.
24. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
25. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.

APPENDIX

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Briumvi Prior Authorization Policy
- Briumvi® (ublituximab-xiiy intravenous infusion – TG Therapeutics)

REVIEW DATE: 11/15/2023

OVERVIEW

Briumvi, a CD20-directed cytolytic antibody, is indicated for the treatment of relapsing forms of **multiple sclerosis** (MS), to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease, in adults.[1]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system that impacts almost 1,000,000 people in the US.[2-4] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses with minimal magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders.[2-4] Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria.

Guidelines

Briumvi is not addressed in guidelines. In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Briumvi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Briumvi as well as the monitoring required for adverse events and long-term efficacy, approval requires Briumvi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Briumvi is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Multiple Sclerosis, Relapsing Forms.** Approve for 1 year if the patient meets one of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets all the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has a relapsing form of multiple sclerosis; AND
       45. Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
     - **iii.** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR
   - **B)** Patient is Currently Receiving Briumvi for ≥ 1 Year. Approve if the patient meets all of the following (i, iii, iii, and iv):
     46. Note: A patient who has received < 1 year of therapy or who is restarting therapy with Briumvi should be considered under criterion 1A (Multiple Sclerosis [Relapsing Forms], Initial Therapy).
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has a relapsing form of multiple sclerosis; AND
       47. Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
     - **iii.** Patient meets one of the following [(1) or (2)]:
       - **(1)** Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
         48. Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability Status Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item Multiple Sclerosis Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.
       - **(2)** Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND
     - **iv.** Medication is prescribed by or in consultation with a neurologist or a physican who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Briumvi is not recommended in the following situations:

73. **Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.** These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

74. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

171. Briumvi® intravenous infusion [prescribing information]. Morrisville, NC: TG Therapeutics; December 2022.
172. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. Updated September 2019. Available at: https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/DMT_Consensus_MS_Coalition.pdf. Accessed on November 14, 2023.
173. McGinley MP, Goldschmidt C, Rae-Grant AD. Diagnosis and treatment of multiple sclerosis. A review. *JAMA*. 2021;325(8):765-779.
174. The Medical Letter on Drugs and Therapeutics. Drugs for multiple sclerosis. *Med Lett Drugs Ther*. 2021;63(1620):42-48.
175. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
176. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.

APPENDIX

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Dalfampridine Prior Authorization Policy
- Ampyra® (dalfampridine extended-release tablets – Acorda, generic)

REVIEW DATE: 11/08/2023

OVERVIEW

Dalfampridine, a potassium channel blocker, is indicated to improve walking in adults with **multiple sclerosis**.[1] This was demonstrated by an increase in walking speed.

Safety

Dalfampridine is contraindicated in patients with a history of seizures; moderate or severe renal impairment (estimated creatinine clearance ≤ 50 mL/min); and in those with a of hypersensitivity to dalfampridine or 4-aminopyridine.[1]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of dalfampridine. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with dalfampridine as well as the monitoring required for adverse events and long-term efficacy, approval requires dalfampridine to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of dalfampridine is recommended in those who meet the following criteria:

FDA-Approved Indication

63. Multiple Sclerosis (MS). Approve for the duration noted below if the patient meets one of the following criteria (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets all of the following (i, ii, iii, iv, and v):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient is ambulatory; AND
- **iii.** Dalfampridine is being used to improve or maintain mobility; AND
- **iv.** Patient has impaired ambulation as evaluated by an objective measure; AND
  Note: Examples of objective measures of ambulation include the Timed 25-Foot Walk and Multiple Sclerosis Walking Scale-12.
- **v.** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR

B) Patient Currently Receiving Dalfampridine. Approve for 1 year of the patient meets all of the following (i, ii, iii, iv, and v):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient is ambulatory; AND
- **iii.** Dalfampridine is being used to improve or maintain mobility; AND

iv. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; AND

v. According to the prescriber the patient has experienced an improvement or maintenance in walking speed or other objective measures related to ambulation.
Note: Examples of objective measures of ambulation include the Timed 25-Foot Walk and Multiple Sclerosis Walking Scale-12.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of dalfampridine is not recommended in the following situations:

75. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

27. Ampyra® extended-release tablets [prescribing information]. Pearl River, NY: Acorda; June 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Dimethyl Fumarate Prior Authorization Policy
- Tecfidera® (dimethyl fumarate delayed-release capsules – Biogen, generic)

REVIEW DATE: 11/08/2023

OVERVIEW

Dimethyl fumarate is indicated for the treatment of patients with relapsing forms of **multiple sclerosis** (MS) to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive MS in adults.[1]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[2-4] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

IN SEPTEMBER 2019, A CONSENSUS PAPER WAS UPDATED BY THE MS COALITION THAT DISCUSSES THE USE OF DISEASE-MODIFYING THERAPIES IN MS.[2] MANY OPTIONS FROM VARIOUS DISEASE CLASSES, INVOLVING DIFFERENT MECHANISMS OF ACTION AND MODES OF ADMINISTRATION, HAVE SHOWN BENEFITS IN PATIENTS WITH MS.

Safety

Progressive multifocal leukoencephalopathy has occurred in patients with MS treated with dimethyl fumarate, including a fatal case.[1]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of dimethyl fumarate. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with dimethyl fumarate as well as the monitoring required for adverse events and efficacy, approval requires dimethyl fumarate to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of dimethyl fumarate is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Multiple Sclerosis.** Approve for the duration noted below if the patient meets one of the following (A or B):

C) Initial Therapy. Approve for 1 year if the patient meets the following (i and ii):

iv. Patient has a relapsing form of multiple sclerosis; AND
Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

v. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR

D) Patient Has Been Receiving Dimethyl Fumarate for ≥ 1 Year. Approve for 1 year if the patient meets the following (i, ii, and iii):

i. Patient has a relapsing form of multiple sclerosis; AND
Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

ii. Patient meets one of the following (a or b):

a) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability State Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item Multiple Sclerosis Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss; OR

b) Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND

iii. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of dimethyl fumarate is not recommended in the following situations:

76. Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis. These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

77. Non-Relapsing Forms of Multiple Sclerosis. The efficacy of dimethyl fumarate has not been established in patients with non-relapsing forms of multiple sclerosis.[1]
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

78. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Fingolimod Prior Authorization Policy
- Gilenya® (fingolimod capsules – Novartis, generic)

REVIEW DATE: 11/08/2023

OVERVIEW

Fingolimod, a sphingosine 1-phosphate receptor modulator, is indicated for the treatment of patients with relapsing forms of **multiple sclerosis** (MS), to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in patients ≥ 10 years of age.[1]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[2-4] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

IN SEPTEMBER 2019, A CONSENSUS PAPER WAS UPDATED BY THE MS COALITION THAT DISCUSSES THE USE OF DISEASE-MODIFYING THERAPIES IN MS.[2] MANY OPTIONS FROM VARIOUS DISEASE CLASSES, INVOLVING DIFFERENT MECHANISMS OF ACTION AND MODES OF ADMINISTRATION, HAVE SHOWN BENEFITS IN PATIENTS WITH MS.[2] THE AMERICAN ACADEMY OF NEUROLOGY HAS PRACTICE GUIDELINES REGARDING DISEASE-MODIFYING THERAPIES FOR ADULTS WITH MS.[7] THE GUIDELINES CITES FINGOLIMOD AS ONE OF THE AGENTS TO CONSIDER FOR PATIENTS WITH MS WHO HAVE HIGHLY ACTIVE DISEASE.

Safety

The initiation of fingolimod leads to decreases in heart rate.[1] After the first dose of fingolimod, the heart rate decreases are noted within an hour and generally are greatest at 6 hours, although the effects can be observed 24 hours after the first dose in some patients. The first dose of fingolimod should be given in a setting with resources to appropriately manage symptomatic bradycardia. Observe patients for 6 hours after

the first fingolimod dose for signs and symptoms of bradycardia. Patients with prolonged QTc interval at baseline or during the observation period, or taking medications with known risks of torsades de pointes, should be observed overnight with continuous electrocardiographic (ECG) monitoring. When restarting fingolimod after discontinuation for more than 14 days after the first treatment month, perform first-dose monitoring. There are several contraindications for use which mainly include patients with background cardiovascular disease. Fingolimod is associated with serious toxicities such as decreased heart rate and/or atrioventricular condition after the first dose; an increased risk of infections; macular edema; pulmonary toxicity; and elevated liver enzymes. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients who were given fingolimod in the postmarketing setting.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of fingolimod. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with fingolimod as well as the monitoring required for adverse events and efficacy, approval requires fingolimod to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of fingolimod is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Multiple Sclerosis.** Approve for the duration noted below if the patient meets one of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets the following (i, ii and iii):
   - **iii.** Patient has a relapsing form of multiple sclerosis; AND
     Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
   - **iv.** Patient is ≥ 10 years of age; AND
   - **v.** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR
   - **B)** Patient is Currently Receiving Fingolimod for ≥ 1 Year. Approve for 1 year if the patient meets the following (i, ii, iii and iv):
   - **v.** Patient has a relapsing form of multiple sclerosis; AND
     Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
   - **vi.** Patient is ≥ 10 years of age; AND
   - **vii.** Patient meets one of the following (a or b):
     - **e)** Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
       Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability State Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale;

reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item MS Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.

f) Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND

viii. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of fingolimod is not recommended in the following situations:

79. Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis. These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

80. Non-Relapsing Forms of Multiple Sclerosis. In the INFORMS trial, fingolimod did not slow disease progression in patients with primary progressive multiple sclerosis.[8]
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

81. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Glatiramer Products Prior Authorization Policy
- Copaxone® (glatiramer acetate subcutaneous injection [20 mg/mL and 40 mg/mL] – Teva, generic)
- Glatopa® (glatiramer acetate subcutaneous injection [20 mg/mL and 40 mg/mL] – Sandoz)

REVIEW DATE: 11/08/2023

OVERVIEW

Copaxone, Glatopa and generic glatiramer acetate are indicated for the treatment of relapsing forms of **multiple sclerosis** (MS) to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease, in adults.[1-3]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[4-6] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders.[4-6] Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[7] as well as in 2017.[8] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[4-8] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[4] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Copaxone (20 mg/mL and 40 mg/mL, generic) and Glatopa (20 mg/mL and 40 mg/mL). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Copaxone/Glatopa as well as the monitoring required for adverse events and long-term efficacy, approval requires Copaxone/Glatopa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of glatiramer is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Multiple Sclerosis.** Approve for the duration noted below if the patient meets one of the following (A or B):
   R) Initial Therapy. Approve for 1 year if the patient meets the following (i and ii):
   ix. Patient has a relapsing form of multiple sclerosis; AND
   Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
   x. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR
   S) Patient is Currently Receiving Glatiramer for ≥ 1 Year. Approve for 1 year if the patient meets the following (i, ii, and iii):
      i. Patient has a relapsing form of multiple sclerosis; AND
      Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
      ii. Patient meets one of the following (a or b):
         g) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
         Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability State Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item MS Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.
         h) Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND
      iii. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of glatiramer is not recommended in the following situations:

27. **Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.** These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

28. **Non-Relapsing Forms of Multiple Sclerosis.** The efficacy of Copaxone and Glatopa have not been established in patients with multiple sclerosis with non-relapsing forms of multiple sclerosis.[1-4]
Note: An example of non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

29. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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28. Glatiramer subcutaneous injection [prescribing information]. Morgantown, WV: Mylan; March 2023.
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APPENDIX

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Kesimpta Prior Authorization Policy
- Kesimpta® (ofatumumab subcutaneous injection – Novartis)

REVIEW DATE: 11/08/2023

OVERVIEW

Kesimpta, a CD20-directed cytolytic antibody, is indicated for the treatment of relapsing forms of **multiple sclerosis** (MS) to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive MS in adults.[1]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[2-4] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders.[2-4] Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Kesimpta. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kesimpta as well as the monitoring required for adverse events and long-term efficacy, approval requires Kesimpta to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kesimpta is recommended in those who meet the following criteria:

FDA-Approved Indication

160. Multiple Sclerosis. Approve for the duration noted below if the patient meets one of the following (A or B):

C) Initial Therapy. Approve for 1 year if the patient meets the following (i, ii, and iii):

xi. Patient has a relapsing form of multiple sclerosis; AND

Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

xii. Patient is ≥ 18 years of age; AND

xiii. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR

D) Patient is Currently Receiving Kesimpta for ≥ 1 Year. Approve for 1 year if the patient meets the following (i, ii, iii, and iv):

i. Patient has a relapsing form of multiple sclerosis; AND

Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

ii. Patient meets one of the following (a or b):

i) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR

Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability State Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item MS Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.

j) Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND

iii. Patient is ≥ 18 years of age; AND

iv. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kesimpta is not recommended in the following situations:

82. Concurrent Use with Other Disease Modifying Agents Used for Multiple Sclerosis. These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

83. Non-Relapsing Forms of Multiple Sclerosis. The efficacy of Kesimpta has not been established in patients with multiple sclerosis with non-relapsing forms of multiple sclerosis.[1]

Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

84. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Lemtrada Prior Authorization Policy
- Lemtrada® (alemtuzumab intravenous infusion – Genzyme)

REVIEW DATE: 11/15/2023

OVERVIEW

Lemtrada, a CD52-directed cytolytic monoclonal antibody, is indicated for the treatment of patients with relapsing forms of **multiple sclerosis** (MS) to include relapsing remitting disease and active secondary progressive MS in adults.[1] Lemtrada is not recommended for use in patients with clinically isolated syndrome because of its safety profile.

Due to its safety profile, use of Lemtrada should generally be reserved for patients who have had an inadequate response to two or more medications indicated for the treatment of MS.[1] Lemtrada contains the same active ingredient found in Campath® (alemtuzumab intravenous infusion). The safety and efficacy of Lemtrada have not been established in patients less than 17 years of age. Lemtrada is administered by intravenous infusion over 4 hours for two or more treatment courses: The dose for the first course is 12 mg/day on five consecutive days. The second course is 12 mg/day on three consecutive days 12 months after the first treatment course. Subsequent treatment courses of 12 mg per day on three consecutive days (36 mg total) may be given, as needed, at least 12 months after the last dose of any prior treatment course.

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system that impacts almost 1,000,000 people in the US.[2-4] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

A practice guideline recommendation regarding disease-modifying agents for adults with MS from the American Academy of Neurology (2018) states to consider Lemtrada for patients with MS who have highly active disease.[7]

Safety

Lemtrada is available only through a restricted Risk Evaluation Mitigation Strategy (REMS) program called the LEMTRADA REMS Program due to the risks of autoimmunity, infusion reactions, stroke, and malignancies.[1] Use of Lemtrada is contraindicated in patients who have infection with human immunodeficiency virus (HIV) and those with active infection. Progressive multifocal leukoencephalopathy has occurred in a patient with MS who received Lemtrada.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lemtrada. All approvals are provided for 30 days which is an adequate duration for the patient to receive the recommended number of doses. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lemtrada, as well as the monitoring required for adverse events and long-term efficacy, approval requires Lemtrada to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Lemtrada at initiation as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, MRI reports, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lemtrada injection is recommended in those who meet the following criteria:

FDA-Approved Indication

2. **Multiple Sclerosis.** Approve for the duration noted if the patient meets one of the following (A or B):
   - **C)** Initial Therapy (this includes patients who have started but not completed the first course of Lemtrada therapy). Approve for five doses in patients who meet all of the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 17 years of age; AND
     - **ii.** Patient has a relapsing form of multiple sclerosis; AND
       Note: Examples of relapsing forms of multiple sclerosis include relapsing remitting disease and active secondary progressive disease.
     - **iii.** Patient meets one of the following (a, b, or c):
       - **a)** According to the prescriber, the patient has experienced inadequate efficacy or significant intolerance to two disease-modifying agents used for multiple sclerosis; OR
         Note: See Appendix for examples.

b) Patient has previously received one of Kesimpta (ofatumumab subcutaneous injection), Tysabri (natalizumab intravenous infusion), Tyruko (natalizumab-sztn intravenous infusion), Briumvi (ublituximab-xiij intravenous infusion), Mavenclad (cladribine tablets), Ocrevus (ocrelizumab intravenous infusion), or Lemtrada; OR

c) According to the prescriber, the patient has highly-active or aggressive multiple sclerosis by meeting one of the following [(1), (2), (3), or (4)]:

(1) Patient has demonstrated rapidly advancing deterioration(s) in physical functioning **[documentation required]**; OR

49. Note: Examples include loss of mobility or lower levels of ambulation and severe changes in strength or coordination.

(2) Disabling relapse(s) with suboptimal response to systemic corticosteroids **[documentation required]**; OR

(3) Magnetic resonance imaging (MRI) findings suggest highly active or aggressive multiple sclerosis **[documentation required]**; OR

50. Note: Examples include new, enlarging, or a high burden of T2 lesions or gadolinium-enhancing lesions.

(4) Manifestations of multiple sclerosis-related cognitive impairment **[documentation required]**; AND

iv. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR

D) Patient Who Has Completed a Previous Course of Lemtrada Therapy. Approve for three doses if the patient meets all of the following (i, ii, iii, iv, and v):

i. Patient is ≥ 17 years of age; AND

ii. Patient has a relapsing form of multiple sclerosis; AND

Note: Examples of relapsing forms of multiple sclerosis include relapsing remitting disease and active secondary progressive disease.

iii. Patient meets one of the following (a or b):

a) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR

Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability Status Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item MS Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.

b) Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND

iv. At least 12 months has elapsed from the last dose of any prior Lemtrada treatment course; AND

v. Medication is prescribed by or in consultation with a neurologist or a physician that specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lemtrada is not recommended in the following situations:

1. **Clinically Isolated Syndrome.** Lemtrada is not recommended for use in patients with clinically isolated syndrome due to its safety profile.[1]

2. **Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.** These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

3. **HIV Infection.** Use of Lemtrada is contraindicated in patients who are infected with HIV because Lemtrada causes prolonged reductions of CD4+ lymphocyte counts.[1]

4. **Non-Relapsing Forms of Multiple Sclerosis.** The efficacy of Lemtrada has not been established in patients with multiple sclerosis with non-relapsing forms of the disease.[1]
   Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

51.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

330. Lemtrada® intravenous infusion [prescribing information]. Cambridge, MA: Genzyme; May 2023.
331. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. September 2019. Available at: http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed on November 10, 2023.
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APPENDIX

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Mavenclad Prior Authorization Policy
- Mavenclad® (cladribine tablets – EMD Serono)

REVIEW DATE: 11/08/2023

OVERVIEW

Mavenclad, a purine antimetabolite, is indicated for the treatment of relapsing forms of **multiple sclerosis** (MS), to include relapsing remitting disease, and active secondary progressive disease, in adults.[1] Due to its safety profile, use of Mavenclad is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternative drug for the treatment of MS.[1] A limitation of use is that Mavenclad is not recommended for use in patients with clinically isolated syndrome because of its safety profile.

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[2-4] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders.[2-4] Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

IN SEPTEMBER 2019, A CONSENSUS PAPER WAS UPDATED BY THE MS COALITION THAT DISCUSSES THE USE OF DISEASE-MODIFYING THERAPIES IN MS.[2] MANY OPTIONS FROM VARIOUS DISEASE CLASSES, INVOLVING DIFFERENT MECHANISMS OF ACTION AND MODES OF ADMINISTRATION, HAVE SHOWN BENEFITS IN PATIENTS WITH MS.

Safety

Mavenclad has a Boxed Warning regarding malignancies and the risk of teratogenicity.[1] Mavenclad may increase the risk of malignancy. Also, Mavenclad is a cytotoxic drug. Special handling instructions and disposal procedures should be followed. There are several contraindications associated with the use of

Mavenclad including: patients with current malignancy; pregnant women, women and men of reproductive potential who do not plan to use effective contraception during Mavenclad dosing and for 6 months after the last dose in each treatment course; human immunodeficiency virus (HIV); active chronic infection (e.g., hepatitis or tuberculosis); of hypersensitivity to cladribine; and women intending to breastfeed on a treatment day in which Mavenclad is administered and for 10 days after the last dose. Warnings and Precautions for Mavenclad include lymphopenia, infections, hematologic toxicity, graft-versus-host disease with blood transfusion, and liver injury.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Mavenclad. All approvals are provided for the duration cited below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Mavenclad as well as the monitoring required for adverse events and long-term efficacy, approval requires Mavenclad to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mavenclad is recommended in those who meet the following criteria:

FDA-Approved Indication

4. Multiple Sclerosis. Approve for the duration noted below if the patient meets one of the following (A or B):

E) Initial Therapy. Approve for 1 year if the patient meets the following (i and ii):

vi. Patient has a relapsing form of multiple sclerosis; AND
Note: Examples of relapsing forms of multiple sclerosis include relapsing remitting disease and active secondary progressive disease.

vii. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR

F) Patient is Currently Receiving Mavenclad for ≥ 1 Year. Approve for 1 year if the patient meets the following (i, ii, and iii):

xiv. Patient has a relapsing form of multiple sclerosis; AND
Note: Examples of relapsing forms of multiple sclerosis include relapsing remitting disease and active secondary progressive disease.

xv. Patient meets one of the following (a or b):

k) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability State Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item MS Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.

l) Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND

xvi. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mavenclad is not recommended in the following situations:

85. Clinically Isolated Syndrome. Mavenclad is not recommended for use in patients with clinically isolated syndrome due to its safety profile.[1]

86. Current Use with Other Disease-Modifying Agents Used for Multiple Sclerosis. These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

87. Non-Relapsing Forms of Multiple Sclerosis. The efficacy of Mavenclad has not been established in patients with multiple sclerosis with non-relapsing forms of the disease.[1]
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

88. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

337. Mavenclad® tablets [prescribing information]. Rockland, MA: EMD Serono; September 2022.
338. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. September 2019. Available at: http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed on November 4, 2023.
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APPENDIX

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Mayzent Prior Authorization Policy
- Mayzent® (siponimod tablets – Novartis)

REVIEW DATE: 11/08/2023

OVERVIEW

Mayzent, a sphingosine 1-phosphate receptor modulator, is indicated for the treatment of relapsing forms of **multiple sclerosis** (MS), to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in adults.[1]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[2-4] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders.[2-4] Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

IN SEPTEMBER 2019, A CONSENSUS PAPER WAS UPDATED BY THE MS COALITION THAT DISCUSSES THE USE OF DISEASE-MODIFYING THERAPIES IN MS.[2] MANY OPTIONS FROM VARIOUS DISEASE CLASSES, INVOLVING DIFFERENT MECHANISMS OF ACTION AND MODES OF ADMINISTRATION, HAVE SHOWN BENEFITS IN PATIENTS WITH MS.

Safety

The initiation of Mayzent leads to decreases in heart rate.[1] First-dose 6-hour monitoring is recommended in certain patients with preexisting cardiac conditions. Additional monitoring beyond 6 hours may also be required. After the initial titration is complete, if Mayzent therapy is interrupted for four or more consecutive daily doses, reinitiate treatment with Day 1 of the titration regimen and also complete first-dose monitoring for patients for whom it is recommended. The most common adverse events with Mayzent include headache, hypertension, and transaminase elevations. Mayzent has Warnings/Precautions

regarding infections, macular edema, bradyarrhythmias and atrioventricular conduction delays, respiratory effects, liver injury, increased blood pressure, and posterior reversible encephalopathy syndrome.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Mayzent. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Mayzent as well as the monitoring required for adverse events and long-term efficacy, approval requires Mayzent to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mayzent is recommended in those who meet the following criteria:

FDA-Approved Indication

5. Multiple Sclerosis. Approve for the duration noted below if the patient meets one of the following (A or B):

A) Initial Therapy. Approve for 1 year if the patient meets the following (i and ii):

viii. Patient has a relapsing form of multiple sclerosis; AND
Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

ix. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR

B) Patient is Currently Receiving Mayzent for ≥ 1 Year. Approve for 1 year if the patient meets the following (i, ii, and iii):

i. Patient has a relapsing form of multiple sclerosis; AND
Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

ii. Patient meets one of the following (a or b):

m) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability State Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item MS Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.

n) Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND

iii. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mayzent is recommended in those who meet the following criteria:

89. Current Use with Other Disease-Modifying Agents Used for Multiple Sclerosis. These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

90. Non-Relapsing Forms of Multiple Sclerosis. The efficacy of Mayzent has not been established in patients with multiple sclerosis with non-relapsing forms of the disease.[1]
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

91. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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344. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. September 2019. Available at: http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed on November 4, 2023.
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APPENDIX

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Ocrevus Prior Authorization Policy
- Ocrevus® (ocrelizumab intravenous infusion – Genentech/Roche)

REVIEW DATE: 11/15/2023

OVERVIEW

Ocrevus is a CD20-directed cytolytic antibody indicated for the treatment of adults with:[1]

- **Relapsing forms of multiple sclerosis** (MS) to include clinically isolated syndrome, relapsing remitting MS, and active secondary progressive MS.
- **Primary progressive MS**.

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system that impacts almost 1,000,000 people in the US.[2-4] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders.[2-4] Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ocrevus. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ocrevus as well as the monitoring required for adverse events and long-term efficacy, approval requires Ocrevus to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ocrevus is recommended in those who meet one of the following criteria:

FDA-Approved Indications

3. Multiple Sclerosis, Relapsing Forms. Approve 1 year if the patient meets one of the following (A or B):

G) Initial Therapy. Approve if the patient meets all the following (i, ii, and iii):

vi. Patient is ≥ 18 years of age; AND

vii. Patient has a relapsing form of multiple sclerosis; AND

52. Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

viii. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR

H) Patient is Currently Receiving Ocrevus for ≥ 1 Year. Approve if the patient meets all of the following (i, ii, iii, and iv):

53. Note: A patient who has received < 1 year of therapy or who is restarting therapy with Ocrevus should be considered under criterion 1A (Multiple Sclerosis [Relapsing Forms], Initial Therapy).

v. Patient is ≥ 18 years of age; AND

vi. Patient has a relapsing form of multiple sclerosis; AND

54. Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

vii. Patient meets one of the following [(1) or (2)]:

(1) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR

55. Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability Status Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item Multiple Sclerosis Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss; OR

(2) Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND

viii. Medication is prescribed by or in consultation with a neurologist or a physican who specializes in the treatment of multiple sclerosis.

56.

59. Multiple Sclerosis, Primary Progressive. Approve for 1 year if the patient meets all of the following (A and B):

58. Patient is ≥ 18 years of age; AND

59. Medication is prescribed by or in consultation with a physician who specializes in the treatment of multiple sclerosis and/or a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ocrevus is not recommended in the following situations:

92. Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis. These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

93. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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178. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. Updated September 2019. Available at: https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/DMT_Consensus_MS_Coalition.pdf. Accessed on November 10, 2023.
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APPENDIX

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Plegridy Prior Authorization Policy
- Plegridy® (peginterferon beta-1a subcutaneous or intramuscular injection – Biogen)

REVIEW DATE: 11/08/2023

OVERVIEW

Plegridy, an interferon beta product, is indicated for the treatment of relapsing forms of **multiple sclerosis** (MS) to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in adults.[1]

Disease Overview

57. MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system that impacts almost 1,000,000 people in the US.[2-4] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

IN SEPTEMBER 2019, A CONSENSUS PAPER WAS UPDATED BY THE MS COALITION THAT DISCUSSES THE USE OF DISEASE-MODIFYING THERAPIES IN MS.[2] MANY OPTIONS FROM VARIOUS DISEASE CLASSES, INVOLVING DIFFERENT MECHANISMS OF ACTION AND MODES OF ADMINISTRATION, HAVE SHOWN BENEFITS IN PATIENTS WITH MS.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Plegridy. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Plegridy as well as the monitoring required for adverse events and long-term efficacy, approval requires Plegridy to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Plegridy is recommended in those who meet the following criteria:

FDA-Approved Indication

2. Multiple Sclerosis. Approve for the duration noted below if the patient meets one of the following (A or B):

T) Initial Therapy. Approve for 1 year if the patient meets the following (i and ii):

xvii. Patient has a relapsing form of multiple sclerosis; AND

Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

xviii. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

U) Patient is Currently Receiving Plegridy for ≥ 1 Year. Approve for 1 year if the patient meets the following (i, ii, and iii):

vii. Patient has a relapsing form of multiple sclerosis; AND

Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

viii. Patient meets one of the following (a or b):

o) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR

Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability State Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item MS Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.

p) Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND

ix. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Plegridy is not recommended in the following situations:

30. Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis. These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

31. Non-Relapsing Forms of Multiple Sclerosis. The efficacy of Plegridy has not been established in patients with multiple sclerosis with non-relapsing forms of multiple sclerosis.[1]

Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

32. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

34. Plegridy® subcutaneous or intramuscular injection [prescribing information]. Cambridge, MA: Biogen; July 2023.
35. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. September 2019. Available at: http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed on November 4, 2023.
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APPENDIX

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Ponvory Prior Authorization Policy
- Ponvory® (ponesimod tablets – Janssen)

REVIEW DATE: 11/08/2023

OVERVIEW

Ponvory, a sphingosine 1-phosphate receptor modulator, is indicated for the treatment of patients with relapsing forms of **multiple sclerosis** (MS), to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in adults.[1]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[2-4] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders.[2-4] Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Ponvory is not addressed. Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ponvory. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ponvory as well as the monitoring required for adverse events and efficacy, approval requires Ponvory to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ponvory is recommended in those who meet the following criteria:

FDA-Approved Indication

2. Multiple Sclerosis. Approve for the duration noted below if the patient meets one of the following (A or B):

C) Initial Therapy. Approve for 1 year if the patient meets the following (i and ii):

x. Patient has a relapsing form of multiple sclerosis; AND
Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

xi. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR

D) Patient is Currently Receiving Ponvory for ≥ 1 Year. Approve for 1 year if the patient meets the following (i, ii, and iii):

i. Patient has a relapsing form of multiple sclerosis; AND
Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

ii. Patient meets one of the following (a or b):

q) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability State Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item MS Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.

r) Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND

iii. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ponvory is not recommended in the following situations:

94. Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis. These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

95. Non-Relapsing Forms of Multiple Sclerosis. The effectiveness of Ponvory in patients with primary progressive multiple sclerosis has not been established.[1]
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

96. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

206. Ponvory® tablets [prescribing information]. Titusville, NJ: Janssen; August 2023.
207. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. September 2019. Available at: http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed on November 4, 2023.
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209. No authors listed. Drugs for multiple sclerosis. *Med Lett Drugs Ther*. 2021;63(1620):42-48.
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APPENDIX

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Rebif Prior Authorization Policy
- Rebif® (interferon beta-1a subcutaneous injection – EMD Serono)

REVIEW DATE: 11/08/2023

OVERVIEW

Rebif is indicated for the treatment of patients with relapsing forms of **multiple sclerosis** (MS) to include clinically isolated syndrome, relapsing remising disease, and active secondary progressive disease in adults.[1]

Disease Overview

~~**58.**~~ MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[2-4] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders.[2-4] Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

IN SEPTEMBER 2019, A CONSENSUS PAPER WAS UPDATED BY THE MS COALITION THAT DISCUSSES THE USE OF DISEASE-MODIFYING THERAPIES IN MS.[2] MANY OPTIONS FROM VARIOUS DISEASE CLASSES, INVOLVING DIFFERENT MECHANISMS OF ACTION AND MODES OF ADMINISTRATION, HAVE SHOWN BENEFITS IN PATIENTS WITH MS.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Rebif. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Rebif as well as the monitoring required for adverse events and long-term efficacy, approval requires Rebif to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rebif is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Multiple Sclerosis.** Approve for the duration noted below if the patient meets one of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets the following (i and ii):
     - **xix.** Patient has a relapsing form of multiple sclerosis; AND
       Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
     - **xx.** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.
   - **B)** Patient is Currently Receiving Rebif for ≥ 1 Year. Approve for 1 year if the patient meets the following (i, ii, and iii):
     - **x.** Patient has a relapsing form of multiple sclerosis; AND
       Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
     - **xi.** Patient meets one of the following (a or b):
       - **s)** Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
         Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability State Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item MS Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.
       - **t)** Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND
     - **xii.** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage is Rebif is not recommended in the following situations:

33. **Concurrent Use with Other Disease-Modifying Agents used for Multiple Sclerosis.** These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

34. Non-Relapsing Forms of Multiple Sclerosis. The efficacy of Rebif has not been established in patients with non-relapsing forms of multiple sclerosis.[1]
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

35. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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41. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. September 2019. Available at: http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed on November 4, 2023.
42. McGinley MP, Goldschmidt C, Rae-Grant AD. Diagnosis and treatment of multiple sclerosis. A review. *JAMA*. 2021;325(8):765-779.
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APPENDIX

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Tascenso ODT Prior Authorization Policy
- Tascenso ODT® (fingolimod orally disintegrating tablets – Cycle/Handa)

REVIEW DATE: 11/08/2023

OVERVIEW

Tascenso ODT, a sphingosine 1-phosphate receptor modulator, is indicated for the treatment of relapsing forms of **multiple sclerosis** (MS), to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in patients ≥ 10 years of age.[1] The FDA-approved dose for pediatric patients ≥ 10 years of age who weigh less than or equal to 40 kg is 0.25 mg once daily. For adults and pediatric patients 10 years of age and older weighing more than 40 kg, the dose is 0.5 mg once daily. Administer Tascenso ODT with or without water. Place the tablet directly on the tongue and allow it to dissolve before swallowing. Tascenso ODT is available in 0.25 mg and 0.5 mg orally disintegrating tablets. Fingolimod doses higher than two times the recommended Tascenso ODT dosage are associated with a greater incidence of adverse events without additional benefit.

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system that impacts almost 1,000,000 people in the US.[2-4] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.[2] The American Academy of Neurology has practice guidelines regarding disease-modifying therapies for adults with MS.[7] The guidelines cites fingolimod as one of the agents to consider for patients with MS who have highly active disease.

Safety
The initiation of Tascenso ODT leads to decreases in heart rate.[1] The first dose of Tascenso ODT should be given in a setting in which resources to appropriately manage symptomatic bradycardia are available. Monitor all patients for 6 hours after the first dose for signs and symptoms of bradycardia with hourly pulse and blood pressure measurement. Patients with prolonged QTc interval at baseline or during the 6-hour observation period, or taking medications with known risks of torsades de pointes, should be observed overnight with continuous electrocardiographic monitoring in a medical facility. When restarting Tascenso ODT after discontinuation for more than 14 days after the first treatment month, perform first-dose monitoring. There are several contraindications for use which mainly include patients with background cardiovascular disease. Tascenso ODT is associated with serious toxicities such as decreased heart rate and/or atrioventricular condition after the first dose; an increased risk of infections; macular edema; pulmonary toxicity; and elevated liver enzymes. Cases of progressive multifocal leukoencephalopathy have occurred in patients with multiple sclerosis who were given fingolimod in the postmarketing setting.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Tascenso ODT. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tascenso ODT as well as the monitoring required for adverse events and efficacy, approval requires Tascenso ODT to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Tascenso ODT is recommended in those who meet the following criteria:

FDA-Approved Indication

3. Multiple Sclerosis. Approve for 1 year if the patient meets one of the following (A or B):
- **E)** Initial Therapy. Approve if the patient meets the following (i, ii, and iii):
  - **xii.** Patient has a relapsing form of multiple sclerosis; AND
    Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
  - **xiii.** Patient is ≥ 10 years of age; AND
  - **xiv.** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR
- **F)** Patient is Currently Receiving Tascenso ODT for ≥ 1 Year. Approve if the patient meets the following (i, ii, iii, and iv):
  - **xxi.** Patient has a relapsing form of multiple sclerosis; AND
    Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
  - **xxii.** Patient is ≥ 10 years of age; AND
  - **xxiii.** Patient meets one of the following (a or b):
    - **u)** Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
      Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing

lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability State Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity (NEDA)-3 or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item MS Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.

v) Patient experienced stabilization, slow progression, or improvement in at least one symptoms such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND

xxiv. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tascenso ODT is not recommended in the following situations:

97. Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis. These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

98. Non-Relapsing Forms of Multiple Sclerosis. In the INFORMS trial fingolimod did not slow disease progression in patients with primary progressive multiple sclerosis.[8]
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

99. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

212. Tascenso ODT™ orally disintegrating tablets [prescribing information]. Cambridge UK and San Jose, CA: Cycle and Handa; August 2023.
213. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. September 2019. Available at: http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed on November 4, 2023.
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215. No authors listed. Drugs for multiple sclerosis. *Med Lett Drugs Ther*. 2021;63(1620):42-48.
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219. Lublin F, Miller DH, Freedman MS, et al, on behalf of the INFORMS Study Investigators. Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomized, double-blind, placebo-controlled trial. *Lancet*. 2016;387:1075-1084.

APPENDIX

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Teriflunomide Prior Authorization Policy
- Aubagio® (teriflunomide tablets – Genzyme/Sanofi, generic)

REVIEW DATE: 11/08/2023

OVERVIEW

Teriflunomide, a pyrimidine synthesis inhibitor, is indicated for the treatment of patients with relapsing forms of **multiple sclerosis** (MS) to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease, in adults.[1]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[2-4] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

IN SEPTEMBER 2019, A CONSENSUS PAPER WAS UPDATED BY THE MS COALITION THAT DISCUSSES THE USE OF DISEASE-MODIFYING THERAPIES IN MS.[2] MANY OPTIONS FROM VARIOUS DISEASE CLASSES, INVOLVING DIFFERENT MECHANISMS OF ACTION AND MODES OF ADMINISTRATION, HAVE SHOWN BENEFITS IN PATIENTS WITH MS.

Safety

Teriflunomide has a Boxed Warning regarding hepatotoxicity and the risk of embryofetal toxicity.[1]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of teriflunomide. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with teriflunomide as well as the monitoring required for adverse events and long-term efficacy, approval requires teriflunomide to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of teriflunomide is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Multiple Sclerosis.** Approve for the duration noted below if the patient meets one of the following (A or B).
   - **E)** Initial Therapy. Approve for 1 year if the patient meets the following (i and ii):
     - **xv.** Patient has a relapsing form of multiple sclerosis; AND
       Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
     - **xvi.** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR
   - **F)** Patient is Currently Receiving Teriflunomide for ≥ 1 Year. Approve for 1 year if the patient meets the following (i, ii, and iii):
     - **xxv.** Patient has a relapsing form of multiple sclerosis; AND
       Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
     - **xxvi.** Patient meets one of the following (a or b):
       - **w)** Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
         Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability State Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item MS Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.
       - **x)** Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND
     - **xxvii.** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of teriflunomide is not recommended in the following situations:

100. Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis. These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

101. Non-Relapsing Forms of Multiple Sclerosis. The efficacy of teriflunomide has not been established in patients with non-relapsing forms of multiple sclerosis.[1]
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

102. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Vumerity Prior Authorization Policy
- Vumerity® (diroximel fumarate delayed-release capsules – Biogen)

REVIEW DATE: 11/08/2023

OVERVIEW

Vumerity is indicated for the treatment of patients with relapsing forms of **multiple sclerosis** (MS) to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive MS in adults.[1]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[2-4] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders.[2-4] Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

IN SEPTEMBER 2019, A CONSENSUS PAPER WAS UPDATED BY THE MS COALITION THAT DISCUSSES THE USE OF DISEASE-MODIFYING THERAPIES IN MS.[2] MANY OPTIONS FROM VARIOUS DISEASE CLASSES, INVOLVING DIFFERENT MECHANISMS OF ACTION AND MODES OF ADMINISTRATION, HAVE SHOWN BENEFITS IN PATIENTS WITH MS.

Safety

Progressive multifocal leukoencephalopathy has occurred in patients with MS treated with dimethyl fumarate delayed-release capsules, which has the same active metabolite as Vumerity.[1]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vumerity. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vumerity as well as the monitoring required for adverse events and efficacy, approval requires Vumerity to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vumerity is recommended in those who meet the following criteria.

FDA-Approved Indication

1. **Multiple Sclerosis.** Approve for the duration noted below if the patient meets one the following (A or B):

E) Initial Therapy. Approve for 1 year if the patient meets the following (i and ii):

xvii. Patient has a relapsing form of multiple sclerosis; AND

Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

xviii. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR

F) Patient is Currently Receiving Vumerity for ≥ 1 Year. Approve for 1 year if the patient meets the following (i, ii, and iii):

xxviii. Patient has a relapsing form of multiple sclerosis; AND

Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

xxix. Patient meets one of the following (a or b):

y) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR

Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability State Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item MS Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.

z) Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND

xxx. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vumerity is not recommended in the following situations:

103. Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis. These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

104. Non-Relapsing Forms of Multiple Sclerosis. The efficacy of Vumerity has not been established in patients with multiple sclerosis with non-relapsing forms of multiple sclerosis.[1]
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

105. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis and Crohn's Disease – Tysabri Prior Authorization Policy
- Tysabri® (natalizumab intravenous infusion – Biogen)

REVIEW DATE: 11/15/2023

OVERVIEW

Tysabri, an integrin receptor antagonist, is indicated for the treatment of:[1]

- Relapsing forms of **multiple sclerosis** (MS) include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in adults as monotherapy.
- **Crohn's disease**, inducing and maintaining clinical response and remission in adults with moderately to severely active disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies and inhibitors of tumor necrosis factor (TNF)-α.

Tysabri increases the risk of progressive multifocal leukoencephalopathy (PML).[1] When initiating and continuing treatment with Tysabri in patients with MS, physicians should consider whether the expected benefit of Tysabri is sufficient to offset the risks. Tysabri should not be used in combination with immunosuppressants (e.g., azathioprine, 6-mercaptopurine, cyclosporine, methotrexate) or inhibitors of TNFα. The safety and effectiveness in patients with MS or Crohn's disease < 18 years of age have not been established.

Disease Overview

Multiple Sclerosis

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system that impacts almost 1,000,000 people in the US.[2] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-4] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria.

Crohn's Disease

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract.[8] The prevalence has been increasing worldwide.[9] Common symptoms of Crohn's disease include abdominal pain, diarrhea, fatigue, weight loss, fever, anemia, and recurrent fistulas. Adults with Crohn's disease may be at risk of bone fractures, as well as thromboembolism. Other extraintestinal manifestations may occur (e.g., primary

sclerosing cholangitis). Younger patients may experience growth failure.[6,7] The chronic intestinal inflammation over time leads to intestinal complications such as strictures, fistulas, and abscesses. Only 20% to 30% of patients with Crohn's disease will have a nonprogressive or indolent course. Therefore, it is appropriate to identify therapies that will achieve adequate control for the patient. Many different therapies are available including corticosteroids, immunomodulators (e.g., azathiopurine, 6-mercaptopurine), and anti-TNF agents (e.g., infliximab products, adalimumab products, Cimzia® [certolizumab pegol subcutaneous injection]).

Guidelines

A practice guideline recommendation regarding disease-modifying agents for adults with MS from the American Academy of Neurology (2018) states to consider Tysabri for patients with MS who have highly active disease.[7]

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various drug classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

The American College of Gastroenterology has guidelines on management of Crohn's disease in adults (2018).[9] Anti-TNF agents (e.g., infliximab products, adalimumab products, Cimzia should be used to treat Crohn's disease that is resistant to treatment with corticosteroids, thiopurines or methotrexate. For patients with moderately to severely active Crohn's disease and objective evidence of active disease, anti-integrin therapy (with Entyvio® [vedolizumab intravenous infusion]) with or without an immunomodulator is more effective than placebo and should be considered for use for induction of symptomatic remission in patients with Crohn's disease. Tysabri is more effective than placebo and should be considered to be used for induction of symptomatic response and remission in patients with active Crohn's disease (strong recommendation; high level of evidence). Tysabri should be used for maintenance of Tysabri-induced remission of Crohn's disease only if serum antibody to John Cunningham virus is negative. Stelara® (ustekinumab subcutaneous injection or intravenous infusion) should be given for moderate to severe Crohn's disease patients who failed treatment with corticosteroids, thiopurines, methotrexate, or anti-TNF agents or who have had no prior exposure to anti-TNF agents.

Safety

Tysabri has a Boxed Warning regarding the risk of PML.[1] Tysabri is available only through a special restricted distribution Risk Evaluation and Mitigation Strategy (REMS) program called the TOUCH® Prescribing Program.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tysabri. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tysabri as well as the monitoring required for adverse events and long-term efficacy, approval requires Tysabri to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Tysabri at initiation for MS as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, magnetic resonance imaging (MRI) reports, and/or other information.
Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tysabri injection is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Multiple Sclerosis.** Approve for 1 year if the patient meets one of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has a relapsing form of multiple sclerosis; AND
       Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive multiple sclerosis.
     - **iii.** Patient meets one of the following (a or b):
       - **a)** According to the prescriber the patient has experienced inadequate efficacy or significant intolerance to one disease-modifying agent used for multiple sclerosis; OR
         Note: See Appendix for examples.
       - **b)** According to the prescriber the patient has highly active or aggressive multiple sclerosis by meeting one of the following [(1), (2), (3), or (4)]:
         - **(5)** Patient has demonstrated rapidly advancing deterioration(s) in physical functioning **[documentation required]**; OR
           59. Note: Examples include loss of mobility or lower levels of ambulation and severe changes in strength or coordination.
         - **(6)** Disabling relapse(s) with suboptimal response to systemic corticosteroids **[documentation required]**; OR
         - **(7)** Magnetic resonance imaging [MRI] findings suggest highly active or aggressive multiple sclerosis **[documentation required]**; OR
           60. Note: Examples include new, enlarging, or a high burden of T2 lesions or gadolinium-enhancing lesions.
         - **(8)** Manifestations of multiple sclerosis-related cognitive impairment **[documentation required]**; AND
     - **iv.** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR
   - **B)** Patient is Currently Receiving Tysabri. Approve if the patient meets one of the following (i or ii):
     - **i.** Patient has been receiving Tysabri for < 1 year. Approve if the patient meets all of the following (a, b, and c):
       - **a)** Patient is ≥ 18 years of age; AND
       - **b)** Patient has a relapsing form of multiple sclerosis; AND
         Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
       - **c)** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR
     - **ii.** Patient has been receiving Tysabri for 1 year or more. Approve if the patient meets all of the following (a, b, c, and d):
       - **a)** Patient is ≥ 18 years of age; AND
       - **b)** Patient has a relapsing form of multiple sclerosis; AND
         Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive multiple sclerosis.
       - **c)** Patient meets one of the following [(1) or (2)]:
         - **a)** Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR

Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability Status Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item Multiple Sclerosis Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.

b) Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND

d) Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

2. Crohn's Disease. Approve for the duration noted below if the patient meets one of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets all of the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Patient has moderately to severely active Crohn's disease; AND

iii. Patient has tried at least two biologics for Crohn's disease; AND

Note: Examples include an adalimumab product (Humira, biosimilars), Cimzia (certolizumab pegol subcutaneous injection), an infliximab intravenous product (Remicade, biosimilars), Zymfentra™ (infliximab-dyyb subcutaneous injection), Entyvio (vedolizumab intravenous infusion), Skyrizi (risankizumab-rzaa intravenous infusion and subcutaneous injection [on-body injector]), Stelara (ustekinzumab subcutaneous injection and intravenous infusion).

Note: Each biosimilar tried from the same chemical would only count as a trial of one product.

iv. Medication is prescribed by or in consultation with a gastroenterologist; OR

B) Patient is Currently Receiving Tysabri. Approve for 1 year if the patient meets all of the following (i, ii, iii, and iv):

i. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient is ≥ 18 years of age; AND

iii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Tysabri); OR

61. Note: Examples of objective measures include fecal markers (e.g., renal lactoferrin, fecal calprotectin), serum markers (e.g., C-reactive protein), imaging studies (magnetic resonance enterography [MRE], computed tomography enterography [CTE]), endoscopic assessment, and/or reduced dose of corticosteroids.

b) Compared with baseline (prior to initiating Tysabri), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or blood in stool; AND

Medication is prescribed by or in consultation with a gastroenterologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tysabri is not recommended in the following situations:

1. **Concurrent Use with an Immunosuppressant Agent in Patient with Crohn's Disease.** Ordinarily, patients who are receiving chronic immunosuppressant or immunomodulatory therapy or who have systemic medical conditions resulting in significantly compromised immune function should not take Tysabri.[1]

62. Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, methotrexate, an infliximab IV product, Zymfentra (infliximab-dyyb subcutaneous injection), an adalimumab product, Cimzia, Entyvio IV, Skyrizi (risankizumab-rzaa intravenous infusion and subcutaneous injection [on-body injector]), Stelara, and Rinvoq (upadacitinib extended-release tablets).

63.

2. **Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.** These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

3. **Non-Relapsing Forms of Multiple Sclerosis.** The safety and efficacy of Tysabri have not been established in patients with primary progressive multiple sclerosis.
   Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

4. **Ulcerative Colitis.** Efficacy data with use of Tysabri are limited.[10]

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Tysabri® intravenous infusion [prescribing information]. Cambridge, MA: Biogen; October 2023.
2. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. Updated September 2019. Available at: https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/DMT_Consensus_MS_Coalition.pdf. Accessed on November 10, 2023.
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APPENDIX

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis and Ulcerative Colitis – Zeposia Prior Authorization Policy
- Zeposia® (ozanimod capsules – Celgene)

REVIEW DATE: 11/08/2023

OVERVIEW

Zeposia, a sphingosine 1-phosphate receptor modulator, is indicated for the following uses:[1]

- Relapsing forms of **multiple sclerosis** (MS), in adults to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
- **Ulcerative colitis** (UC), in adults with moderately to severely active disease.

Guidelines/Clinical Efficacy

Published guidelines address recommended treatments for the following conditions:

- **Multiple sclerosis (MS):** Zeposia is not currently addressed in MS guidelines. In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various pharmacologic classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.
- **Ulcerative colitis (UC):** Zeposia is not currently addressed in UC guidelines. The American Gastroenterological Association (2020) and the American College of Gastroenterology (2019) have clinical practice guidelines on the management of moderate to severe UC and make recommendations for induction and maintenance of remission in adults.[3,4] Both endorse the use of biologic agents and give specific patient circumstances in the selection for induction and maintenance therapies. The 10-week, induction pivotal trial for Zeposia included adult patients with moderately to severely active UC who had an inadequate response or were intolerant to any of the following agents: oral aminosalicylates, corticosteroids, immunomodulators (e.g., 6-mercaptopurine and azathioprine), or a biologic (e.g., tumor necrosis factor inhibitor, Entyvio [vedolizumab injection]).[1]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zeposia. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zeposia as well as the monitoring required for adverse events and long-term efficacy, approval requires Zeposia to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Zeposia is recommended in those who meet one of the following criteria:

FDA-Approved Indications

6. Multiple Sclerosis. Approve for the duration noted below if the patient meets one of the following (A or B):

A) Initial Therapy. Approve for 1 year if the patient meets the following (i and ii):

xix. Patient has a relapsing form of multiple sclerosis; AND

Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

xx. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR

B) Patient is Currently Receiving Zeposia for ≥ 1 Year. Approve for 1 year if the patient meets the following (i, ii, and iii):

xxxi. Patient has a relapsing form of multiple sclerosis; AND

Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

xxxii. Patient meets one of the following (a or b):

aa) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR

Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability State Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item MS Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.

bb) Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND

xxxiii. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

7. Ulcerative Colitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

F) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient has had a trial of ONE systemic agent for ulcerative colitis; AND

Note: Examples of systemic agents for ulcerative colitis include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone, methylprednisolone. A trial of one biologic also counts as a trial of one systemic agent for ulcerative colitis. Refer to the Appendix A for examples of biologics used for ulcerative colitis.

iii. The medication is prescribed by or in consultation with a gastroenterologist.

I) Patient is Currently Receiving Zeposia. Approve for 1 year if the patient meets BOTH of the following (i and ii):

ix. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of assessment for inflammatory response include fecal markers (e.g., fecal calprotectin), serum markers (e.g., C-reactive protein), endoscopic assessment, and/or reduced dose of corticosteroids.

f) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or decreased rectal bleeding.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zeposia is not recommended in the following situations:

106. Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis. These agents are not indicated for use in combination (see Appendix B for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

107. Non-Relapsing Forms of Multiple Sclerosis. The efficacy of Zeposia has not been established in patients with multiple sclerosis with non-relapsing forms of the disease.[1]
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

108. Concurrent Use with a Biologic or with a Targeted Synthetic Disease-modifying Antirheumatic Drug (DMARD) for Ulcerative Colitis. In the pivotal trials, patients who received Zeposia were not to receive concomitant treatment with non-corticosteroid immunosuppressive or immune-modulating therapies used for the treatment of ulcerative colitis (see Appendix A for examples).[1] Combination therapy is generally not recommended due to a potential for a higher rate of adverse effects with combinations and lack of evidence supporting additive efficacy. There are no data evaluating combination of Zeposia with a targeted synthetic DMARD (e.g., Xeljanz/Xeljanz XR (tofacitinib tablets, oral solution, and extended-release tablets); therefore, safety and efficacy of this combination is unknown.

109. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX A

[*] Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2; S1P – Sphingosine 1-phospate receptor modulator.

APPENDIX B

PRIOR AUTHORIZATION POLICY

POLICY: Muscular Dystrophy – Amondys 45 Prior Authorization Policy
- Amondys 45™ (casimersen intravenous infusion – Sarepta)

REVIEW DATE: 02/15/2023

OVERVIEW

Amondys 45, an antisense oligonucleotide, is indicated for the treatment of **Duchenne muscular dystrophy** (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping.[1] This indication was granted accelerated approval based on an increase in dystrophin in skeletal muscle observed in patients treated with Amondys 45. The prescribing information notes that continued FDA-approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.

Guidelines

Amondys 45 is not addressed in the guidelines for the diagnosis and management of DMD available from the DMD Care Considerations Working Group (2018).[2] Glucocorticoids slow decline in muscle strength and function in DMD and should be considered for all patients with DMD. Exondys 51 (eteplirsen intravenous infusion) is mentioned as an emerging product, approved by an accelerated pathway for those with a mutation in the dystrophin gene amenable to exon 51 skipping.

POLICY STATEMENT

The prescribing information for Amondys 45 states that approval is based on dystrophin production in a limited number of patients (n = 27 treated with Amondys 45) with DMD, but continued approval may be contingent upon a confirmatory trial. Due to inadequate clinical efficacy data, **approval is not recommended** for Amondys 45.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Amondys 45 is not recommended in the following situations:

1. **Duchenne Muscular Dystrophy.** Approval is not recommended due to the unclear clinical benefit of Amondys 45 and lack of clinical efficacy data. Shortcomings of the clinical data with Amondys 45 are numerous. In the pivotal trial, a minimal increase in dystrophin level was noted, but has not been correlated with a clinical benefit. Available data from the pivotal study did not provide any information to determine if Amondys 45 provides a benefit in regard to cardiac and respiratory complications which contribute greatly to morbidity and mortality in patients with DMD. Further, there are concerns of renal toxicity with utilization of Amondys 45, and available data do not support optimal timing for initiation or discontinuation of Amondys 45. Amondys 45 has not been proven to alter or delay disease progression in patients with DMD amenable to exon 45 skipping. A systematic review and meta-analysis of other exon skipping therapies (i.e., Exondys 51, drisapersen) did not show benefit of these

therapies for DMD.[3] The FDA has required a post-marketing trial to verify the clinical efficacy of Amondys 45; patients are still being recruited for the pivotal Phase III ESSENCE study, to further evaluate safety and efficacy in ambulatory boys with DMD.[4]

Amondys 45 is under evaluation in one ongoing, Phase III pivotal study (ESSENCE) in patients with DMD amenable to exon 45 skipping.[1] The primary endpoint is the effect of Amondys 45 on the change from baseline in the total distance walked during the 6-Minute Walk Test (6MWT) at Week 96.[4] Functional outcomes are among the secondary endpoints. In an interim analysis from 43 evaluable patients (n = 27 treated with Amondys 45; n = 16 treated with placebo), the proportion of normal dystrophin protein level was higher at Week 48 with Amondys 45 (1.74% of normal at Week 48 vs. 0.93% of normal at baseline) vs. placebo (0.76% of normal at Week 48 vs. 0.54% of normal at baseline) [P = 0.004 for Amondys 45 vs. placebo).[1] Results from the primary endpoint (6MWT) and functional outcomes have not been reported.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Muscular Dystrophy – Emflaza Prior Authorization Policy
- Emflaza™ (deflazacort tablets and oral suspension – PTC Therapeutics)

REVIEW DATE: 02/15/2023

OVERVIEW

Emflaza is a corticosteroid indicated for the treatment of patients ≥ 2 years of age with **Duchenne muscular dystrophy** (DMD).[1] The efficacy and safety of Emflaza have not been established in patients < 2 years of age.

Disease Overview

DMD is an X-linked recessive disease affecting 1 in 3,600 to 6,000 newborn male infants.[2] The disease is attributed to large frame-shift deletions in the DMD gene (chromosome Xp21) which lead to loss of a structural protein of muscle cells (dystrophin).[3] Females carriers are usually asymptomatic but some may show mild symptoms.[2] Most patients present with symptoms of DMD between the ages of 3 and 5 years. There are wide variances in how quickly DMD progresses, but without intervention death is at approximately 19 years of age.[2-3] With respiratory, cardiac, orthopedic and rehabilitative interventions and use of corticosteroids, children born today can have a life expectancy of up to 40 years.

Clinical Efficacy

The efficacy and safety of Emflaza were established in two pivotal trials in boys with DMD who were ≥ 5 years of age.[4-5] In one study, treatment consisted of Emflaza 0.9 mg/kg/day, Emflaza 1.2 mg/kg/day, or prednisone 0.75 mg/kg/day (n = 196).[4] The primary efficacy analysis, mean change from baseline to Week 12 in average muscle strength (assessed by modified Medical Research Council [MRC]), demonstrated a significant least squares (LS) mean difference in favor of active treatment vs. placebo: Emflaza 0.9 mg/kg/day (0.25 vs. -0.1, P = 0.17), Emflaza 1.2 mg/kg/day (0.36 vs. -0.1, P = 0.0003), and prednisone 0.75 mg/kg/day (0.37 vs. -0.1, P = 0.0002). Adverse events (AEs) differed between prednisone and Emflaza treatment groups. Cushingoid appearance (69.4%), erythema (41.8%), and hirsutism (39.3%) were observed in a numerically greater proportion of patients in the prednisone group compared with either dose of Emflaza. Central obesity was reported in a statistically significant greater proportion of patients treated with prednisone vs. Emflaza. Psychiatric AEs were generally reported at a higher rate in the prednisone group compared with both Emflaza groups.

Guidelines

There are guidelines for the diagnosis and management of DMD available from the DMD Care Considerations Working Group (updated 2018).[6] Dystrophin gene deletion and duplication testing are usually the first test done to confirm a diagnosis of DMD. If deletion/duplication testing is negative, dystrophin gene sequencing is done to look for remaining types of mutations. If genetic testing does not confirm a diagnosis of DMD, then a muscle biopsy should be performed to test for the presence of dystrophin protein. These guidelines additionally discuss the benefits of glucocorticoids in patients with DMD. These benefits include the loss of ambulation at a later age, preservation of upper limb and respiratory function, and avoidance of scoliosis surgery. Although the benefits of glucocorticoids are well established, based on available data, there is uncertainty about which specific products and doses are best.[6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Emflaza. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and

diagnosis of patients treated with Emflaza as well as the monitoring required for adverse events and long-term efficacy, approval requires Emflaza to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Emflaza as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Emflaza is recommended in those who meet the following criteria:

FDA-Approved Indication

60. Duchenne Muscular Dystrophy. Approve for 1 year if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve if the patient meets the following criteria (i, ii, iii, and iv):

- **i.** Patient is 2 years of age and older; AND
- **ii.** Patient's diagnosis of Duchenne Muscular Dystrophy is confirmed by one of the following (a or b) **[documentation required]**:
  - **a)** Genetic testing with a confirmed pathogenic or likely pathogenic variant in the dystrophin gene; OR
  - **b)** Muscle biopsy showing the absence of, or marked decrease in, dystrophin protein; AND
- **iii.** Patient meets ONE of the following conditions (a or b):
  - **a)** Patient has tried prednisone or prednisolone for ≥ 6 months **[documentation required]** AND according to the prescriber, the patient has had at least one of the following significant intolerable adverse effects [1, 2, 3, or 4]:
    - **1)** Cushingoid appearance **[documentation required]**; OR
    - **2)** Central (truncal) obesity **[documentation required]**; OR
    - **3)** Undesirable weight gain defined as ≥ 10% of body weight gain increase over a 6-month period **[documentation required]**; OR
    - **4)** Diabetes and/or hypertension that is difficult to manage according to the prescriber **[documentation required]**; OR
  - **b)** According to the prescriber, the patient has experienced a severe behavioral adverse event while on prednisone or prednisolone therapy that has or would require a prednisone or prednisolone dose reduction **[documentation required]**.
- **iv.** The medication is prescribed by or in consultation with a physician who specializes in the treatment of Duchenne muscular dystrophy and/or neuromuscular disorders.

B) Patient is Currently Receiving Emflaza. Approve if the patient meets the following criteria (i, ii, and iii):

- **i.** Patient has tried prednisone or prednisolone **[documentation required]**; AND
- **ii.** According to the prescriber, the patient has responded to or continues to have improvement or benefit from Emflaza therapy **[documentation required]**; AND
  Note: Examples of improvement or benefit from Emflaza therapy would include improvements in motor function (time from supine to standing, time to climb four stairs, time to run or walk 30 feet), improvement in muscle strength, improve pulmonary function, etc.
- **iii.** The medication is prescribed by or in consultation with a physician who specializes in the treatment of Duchenne muscular dystrophy and/or neuromuscular disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Emflaza is not recommended in the following situations:

110. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Muscular Dystrophy – Exondys 51 Prior Authorization Policy
- Exondys 51™ (eteplirsen intravenous infusion – Sarepta)

REVIEW DATE: 04/26/2023

OVERVIEW

Exondys 51, an antisense oligonucleotide, is indicated for the treatment of **Duchenne muscular dystrophy** (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.[1] Exondys 51 was approved for this indication under accelerated approval based on an increase in dystrophin observed in the skeletal muscle of some patients who received the drug. However, a clinical benefit of Exondys has not been established. The prescribing information notes that continued FDA-approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

Disease Overview

64. DMD is an X-linked recessive disease affecting 1 in 3,600 to 6,000 newborn male infants.[2] The disease is attributed to large frame-shift deletions in the DMD gene (chromosome Xp21) which leads to a loss of the structural protein of muscle cells (dystrophin).[3] Exondys 51 is an antisense oligonucleotide designed to bind to exon 51 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 51 skipping.[1] These patients represent approximately 13% of all patients with DMD.[5]

Guidelines

There are guidelines for the diagnosis and management of DMD available from the DMD Care Considerations Working Group (2018).[4] Genetic testing for a DMD mutation in a blood sample is always required. By fully characterizing the mutation, the predicted effect on the reading frame can be identified, which is the major determinant of phenotype and will determine eligibility for mutation-specific clinical trials. In patients with no mutation identified but with signs/symptoms of DMD, a muscle biopsy is clinically indicated. Glucocorticoids slow decline in muscle strength and function in DMD. Use of corticosteroids reduces the risk of scoliosis and stabilizes pulmonary function. Continued treatment after the patient loses ambulation provides a reduction in the risk of progressive scoliosis and stabilization of pulmonary function tests. Therefore, glucocorticoids should be considered for all patients with DMD. Exondys 51 is mentioned as an emerging product, approved by an accelerated pathway for those with a mutation in the dystrophin gene amenable to exon 51 skipping.

POLICY STATEMENT

Due to the lack of clinical efficacy data, **approval is not recommended** for Exondys 51.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Exondys 51 has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions:

1. **Duchenne Muscular Dystrophy (DMD).** Approval is not recommended due to the unclear clinical benefit of Exondys 51 and lack of clinical efficacy data. Shortcomings of the clinical data with Exondys 51 are numerous. In the pivotal trials, an increase in dystrophin was observed in a very limited number of patients treated with Exondys 51 and the significance of the increase could not be correlated with clinical benefit. Further, the increase in dystrophin was limited by methodological shortcomings which cast doubt on the reliability of biopsies taken during the first 48 weeks of the pivotal trials. Additional limitations of the data include that the pivotal trials only evaluated Exondys 51 in ambulatory patients; therefore, it is unknown if patients with more advanced disease and greater muscle deterioration would derive any benefit from treatment. There is inadequate information available to determine if Exondys 51 provides a benefit regarding cardiac and respiratory complications which greatly contribute to the morbidity and mortality of patients with DMD. Exondys 51 has not been proven to alter or delay disease progression in patients with DMD amenable to exon 51 skipping. The prescribing information for Exondys 51 states that a clinical benefit has not been established.[1] Furthermore, a systematic review and meta-analysis does not show benefit of exon-skipping therapies for DMD.[10] FDA has required a randomized, controlled trial evaluation post-marketing to establish efficacy of Exondys 51. The anticipated study completion is February 2026.[13]

   The efficacy of Exondys 51 was evaluated in open-label studies in patients with DMD that is amenable to exon 51 skipping.[1,6-9,11] One study (n = 12) assessed the effect of Exondys 51 on dystrophin and the potential clinical benefit; however, there was insufficient information on dystrophin levels prior to treatment so it is not possible to estimate a treatment effect on dystrophin levels. The adjusted mean change in the 6-minute walk test (6MWT) from baseline to Week 24 was -25.8 (± 30.6) meters for placebo; -128.2 (± 31.6) meters for Exondys 51, 30 mg/kg; and -0.3 (± 31.2) meters for Exondys 51, 50 mg/kg. An extension of this study evaluated the same patients and compared disease progression with matched historical controls; at Month 36 the difference in 6MWT distance for Exondys 51 vs. historical control was 121 meters in favor of the Exondys 51 cohort (P = 0.028). Over 36 months, ambulation was lost in 16.7% of patients (n = 2/12) treated with Exondys 51 vs. 46.2% of patients (n = 6/13) in the historical control cohort. The average dystrophin protein level after 180 weeks of treatment with Exondys 51 was 0.93% of the dystrophin level in healthy subjects. But because there was insufficient information on baseline dystrophin levels prior to treatment, it is not possible to estimate a treatment effect. Following 240 weeks of treatment, the percent predicted forced vital capacity (FVC%p) was a decrease of 2.3% per year with Exondys 51 compared with a decrease of 4.1% in a natural history cohort.[11] In patients treated with Exondys 51, the percent predicted maximum inspiratory pressure (MIP%p) decreased by 1% per year, and the percent predicted maximum expiratory pressure (MEP%p) decreased by 2.6% per year. However, MIP and MEP were not assessed in the natural history cohort. Another study included 12 new patients with DMD and reports only on the effect of Exondys 51 on dystrophin levels; further clinical efficacy data are not yet available for these 12 patients.[7-9] After 48 weeks of treatment with Exondys 51 the dystrophin level was 0.44% ± 0.43% of the dystrophin level in healthy subjects (P < 0.05). The median increase after 48 weeks was 0.1%.

   The PROMOVI trial was a Phase III, multicenter, open-label, non-randomized trial evaluating the efficacy and safety of Exondys 51 in patients 7 to 16 years of age with DMD and genetic deletions amenable to exon 51 skipping (n = 79).[12] At Week 96, mean 6MWT distance and mean FVC%p decreased from baseline. The results were consistent with Phase II trials of Exondys 51. Several study limitations including the open-label design with lack of a placebo-control group, lack of a prospective, mutation-matched untreated control arm, lack of data on treatment effects in patients earlier in the disease course were not addressed.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Muscular Dystrophy – Gene Therapy – Elevidys Prior Authorization Policy
- Elevidys® (delandistrogene moxeparvovec-rokl intravenous infusion – Sarepta)

REVIEW DATE: 07/19/2023

OVERVIEW

Elevidys, an adeno-associated virus (AAV) vector-based gene therapy, is indicated for the treatment of ambulatory pediatric patients aged 4 through 5 years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the *DMD* gene.[1] This indication is approved under accelerated approval based on expression of Elevidys micro-dystrophin observed in patients treated with Elevidys. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Disease Overview

DMD is a rare, progressive X-linked disease resulting from mutation(s) of the *DMD* gene, also known as the *Dystrophin* gene.[2-4] The incidence of DMD in the US is approximately 1 in 5,000 live male births. The *DMD* gene is the largest known human gene, totaling 2.3 megabases in size. The gene encodes for a functional dystrophin protein, which is part of a transmembrane protein complex that spans the sarcolemma of skeletal and cardiac muscle cells. This complex links the cytoskeleton to the extracellular matrix providing structural integrity to the sarcolemma and helps to transmit and absorb the shock associated with muscle contraction. Mutations in the *DMD* gene prevent the production of functional dystrophin protein or dystrophin is minimally produced. Without dystrophin, normal activity in patients with DMD causes excessive damage to muscle fiber cells. Over time, the muscle cells are replaced with fat and fibrotic tissue. Progressive muscle weakness is the primary manifestation of DMD. This leads to loss of ambulation, associated motor delays, respiratory impairment, and progressive decline in cardiac function. The first clinical symptoms of DMD are delay in motor development milestones, such as walking, which is observed around 2 years of age. Often there is a delay in diagnosis until the age of 3 to 5 years. Age is an important prognostic factor in the progression of DMD. There is no cure for DMD currently. The goal of treatment is to manage symptoms, slow disease progression, and to delay disability. Boys with DMD typically lose the ability to walk by age 12 or 13 years. In the past, mortality occurs by late adolescence or early twenties, however with advances in respiratory and cardiac management, some patients are living into the fourth decade. The most common cause of death for patients with DMD are respiratory failure, respiratory infection, cardiomyopathy, and cardiac arrhythmias. Corticosteroids are a mainstay of therapy in DMD; however, its mechanism of action in DMD is unknown. Corticosteroids ameliorate the symptoms of the disease and delay time to loss of ambulation and other sequelae. Four anti-sense oligonucleotide therapies (exon-skipping) have been approved by the FDA: Exondys 51® (eteplirsen intravenous infusion), Vyondys 53™ (golodirsen intravenous infusion), Viltepso™ (viltolarsen intravenous infusion), and Amondys 45™ (casimersen intravenous infusion). The clinical benefit of these exon-skipping therapies remains unknown since none of the confirmatory clinical studies have been completed.

Clinical Efficacy

The efficacy of Elevidys was evaluated in two studies:[1-4] a Phase II study and a Phase Ib study.[1] Both studies are unpublished and long-term follow-up is ongoing. The Phase II study (n = 41) included two parts: Part I was a 48-week randomized, double-blind, placebo-controlled study in which patients received a single-dose of Elevidys (n = 20) or placebo (n = 21); in Part II, patients treated with placebo in Part I received Elevidys. Patients in this study were stratified by age (age 4 to 5 years vs. age 6 to 7 years) at

randomization. Retrospective analysis identified that 60% of patients in Part I received a dose lower than Elevidys 1.33 x 10^{14} vector genomes (vg)/kg, due to variability in quantification methods.[1-3] In Part I, only 8 patients received the approved dose of Elevidys 1.33 x 10^{14} vg/kg; 12 patients received one-half to two-thirds of the approved dose. In Part II, all patients from the placebo group received the recommended dose of Elevidys 1.33 x 10^{14} vg/kg.

Guidelines

Elevidys is not addressed in current guidelines for DMD. The guidelines from the DMD Care Considerations Working Group (2018) notes that genetic testing for confirming DMD diagnosis is always required.[5-7] In patients with no mutations identified, but with signs/symptoms of DMD, a muscle biopsy is clinically indicated. Glucocorticoids and physical therapy are the mainstays of treatment and should be continued even after the patient is non-ambulatory. Corticosteroids reduce the risk of scoliosis and stabilizes pulmonary function. In patients who are non-ambulatory, continuing corticosteroid treatment provides a reduction in the risk of progressive scoliosis and stabilization of pulmonary function tests. Due to this benefit, glucocorticoids should be considered in all patients with DMD.

Safety

Elevidys is contraindicated in patients with any deletion in exon 8 and/or exon 9 in the *DMD* gene.[1] Warnings/Precautions are for acute serious liver injury, immune-mediated myositis, myocarditis, and pre-existing immunity against AAVrh74. For administration of Elevidys, the anti-AAVrh74 total antibody binding titer should be < 1:400.

POLICY STATEMENT

Due to the lack of clinical efficacy data, **approval is not recommended** for Elevidys.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Elevidys clinical data are limited and available data are not supportive of general approval for the following conditions:

241. Duchenne Muscular Dystrophy (DMD). Approval is not recommended due to the unclear clinical benefit of Elevidys.[1-4] Elevidys clinical trials had numerous study limitations.[1-4] In the Phase II study, Part I, the only double-blind, placebo-controlled part of the clinical trials, only 40% of the patients randomized to Elevidys (n = 8/20) received the intended gene therapy dose. The other clinical trial was a Phase Ib study that was limited by a single-arm, open-label design. In both these trials, the primary efficacy measure was the change in micro-dystrophin expression level from baseline to Week 12. It is unknown whether increases in micro-dystrophin expression will correlate with clinically meaningful functional improvements. Micro-dystrophin is a novel synthetic protein that is much smaller in size compared with that of the dystrophin protein. So although there was about a 40% increase (compared to control) in micro-dystrophin expression from baseline to post-Elevidys infusion, especially in the Phase II study, this did not translate to an increase in the functional scores, as assessed by the North Star Ambulatory Assessment (NSAA). There is no established baseline minimal percentage expression of micro-dystrophin required to show functional changes in DMD. In the

double-blind study, only the subgroup of patients 4 through 5 years of age demonstrated an improvement in the NSAA total score at Week 48 compared with placebo. The subgroup of patients 6 through 7 years of age had a decrease in the NSAA total score compared with placebo, which is contrary to the expected result. Based on this uncompelling NSAA data, the FDA narrowed the age indication for Elevidys to 4 through 5 years, instead of the overall study population (age 4 through 7). Due to this age limitation, the micro-dystrophin primary endpoint in this FDA-approved group, could only be assessed in 3 patients. In the Phase Ib study there was an increase of 4 points in the NSAA total score from baseline to Week 52 in the cohort of patients (n = 20) that received Elevidys. However, the interpretation of data are limited in this study due to its open-label, single-arm design. EMBARK is a randomized, placebo-controlled, double-blind Phase III study with Elevidys that is ongoing. The preliminary results from this study are expected at the end of 2023.

242. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Muscular Dystrophy – Viltepso Prior Authorization Policy
- Viltepso™ (viltolarsen intravenous infusion – Nippon Shinyaku)

REVIEW DATE: 08/30/2023

OVERVIEW

Viltepso, an antisense oligonucleotide, is indicated for the treatment of **Duchenne muscular dystrophy** (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.[1] This indication was granted accelerated approval based on an increase in dystrophin in skeletal muscle observed in patients treated with Viltepso. The prescribing information notes that continued FDA approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.

- Viltepso is an antisense oligonucleotide designed to bind to exon 53 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 53 skipping.[1] These patients represent up to 10% of all patients with DMD.[2] This genetic manipulation intends to restore the reading frame of the resulting mRNA. The result would be production of a shortened, but partially functional dystrophin protein as seen in less severe forms of muscular dystrophy (e.g., Becker muscular dystrophy). Of note, the reading frame of certain deletions (e.g., exon 52 deletions) can be restored by skipping either exon 51 or exon 53.[3] Approximately 8% of mutations are amenable to skipping exon 53 with Viltepso but are not amenable to skipping of exon 51.
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Guidelines

Viltepso and other exon 53 skipping therapies are not addressed in guidelines for DMD. There are guidelines for the diagnosis and management of DMD available from the DMD Care Considerations Working Group (2018).[4] Genetic testing for a DMD mutation in a blood sample is always required. By fully characterizing the mutation, the predicted effect on the reading frame can be identified, which is the major determinant of phenotype and will determine eligibility for mutation-specific clinical trials. In patients with no mutation identified but with signs/symptoms of DMD, a muscle biopsy is clinically indicated. Glucocorticoids slow decline in muscle strength and function in DMD. Use of corticosteroids reduces the risk of scoliosis and stabilizes pulmonary function. Continued treatment after the patient loses ambulation provides a reduction in the risk of progressive scoliosis and stabilization of pulmonary function tests. Therefore, glucocorticoids should be considered for all patients with DMD. Exondys® 51 (eteplirsen intravenous infusion) is mentioned as an emerging product, approved by an accelerated pathway for those with a mutation in the dystrophin gene amenable to exon 51 skipping.

POLICY STATEMENT

The prescribing information for Viltepso states that approval is based on dystrophin production in a limited number of patients (n = 8 treated with the approved dose) with DMD, but approval may be contingent upon a confirmatory trial. Due to inadequate clinical efficacy data, **approval is not recommended** for Viltepso.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Viltepso is not recommended in the following situations:

1. **Duchenne Muscular Dystrophy (DMD).** Approval is not recommended due to the unclear benefit of Viltepso and lack of clinical efficacy data. Shortcomings of the clinical data with Viltepso are numerous. Although the pivotal study demonstrated a measurable increase in dystrophin levels, the significance of this small change has not yet been correlated with a clinical benefit. Data from the pivotal study did not provide any information to determine if Viltepso provides a benefit in regard to cardiac and respiratory complications which contribute greatly to morbidity and mortality in DMD. The pivotal data are also lacking robust functional outcomes related to motor function. Viltepso has not been proven to alter or delay the disease progress in patients with DMD amenable to exon 53 skipping. A systemic review and meta-analysis of other exon skipping therapies (i.e., Exondys 51, drisapersen) does not show benefit of these therapies for DMD.[5] The prescribing information notes that continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.[1] FDA has required a post-marketing trial to verify clinical efficacy of Viltepso. Thus, patients are being recruited for the Phase III RACER53 study, to further evaluate safety and efficacy of Viltepso in 74 ambulatory patients with DMD.

   Viltepso is under evaluation in one ongoing Phase II pivotal study in patients with DMD amenable to exon 53 skipping.[6] The primary endpoint is the effect of Viltepso on dystrophin as a surrogate outcome marker. Functional outcomes were among the secondary endpoints and were compared with a natural history cohort controlled for age, functional status, geographic location, and glucocorticoid treatment status. In this pivotal study (n = 16), the proportion of normal dystrophin protein level was higher at Week 25 (0.6% of normal at baseline vs. 5.9% of normal at Week 24 biopsy). Some functional outcomes were significantly improved from baseline with Viltepso vs. the natural history cohort (time to run walk 10 meters [0.23 meters/second vs. -0.04 meters/second], time to stand from supine [-0.19 seconds vs. 0.66 seconds], and distance on the 6-minute walk test [28.9 meters vs. -65.3 meters]). However, velocity in the time to stand from supine test, time to climb 4 stairs test, North Star Ambulatory Assessment test, and measures of muscle strength by isometric testing were not significantly different from the control group. Data from the long-term extension (out to 109 weeks) of the pivotal trial have been published.[7] All 16 patients who completed the Phase II trial continued into the long-term extension. Functional outcomes (time to stand and time to walk/run 10 meters) were maintained in the Viltepso group over 109 weeks while they were worsened in the natural history cohort. The time to climb 4 stairs was not significantly different from the natural cohort over the 109 weeks. Final results from the 192-week long-term extension study (4 years post-treatment) showed stabilization of motor function over the first 2 years for the primary endpoint of time to stand and significant slowing of motor function loss (compared to historical control groups) over the following 2 years.[8] Similar results were observed with time to run/walk. Time to climb results were not significantly different between Viltepso and control groups.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Muscular Dystrophy – Vyondys 53 Prior Authorization Policy
- Vyondys 53™ (golodirsen intravenous infusion – Sarepta)

REVIEW DATE: 12/13/2023

OVERVIEW

Vyondys 53, an antisense oligonucleotide, is indicated for the treatment of **Duchenne muscular dystrophy** (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.[1] Vyondys 53 was approved for this indication under accelerated approval based on an increase in dystrophin observed in the skeletal muscle of patients who received the drug. The Prescribing Information notes that continued FDA-approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

Disease Overview

DMD is an X-linked recessive disease affecting 1 in 3,600 to 6,000 newborn male infants.[2] The disease is attributed to large frame-shift deletions in the DMD gene (chromosome Xp21) which lead to loss of a structural protein of muscle cells (dystrophin).[3] Over 4,700 mutations on the DMD gene have been identified which lead to a deficiency in production of dystrophin.[2] Therefore, the type of mutation and its effect on the production of dystrophin accounts for the variable phenotypic expression.[4] Female carriers are usually asymptomatic but some may show mild symptoms.[2] There are wide variances in how quickly DMD progresses, but without intervention death is at approximately 19 years of age.[2-4] With respiratory, cardiac, orthopedic and rehabilitative interventions, and use of corticosteroids, children born today can have a life expectancy of up to 40 years.

Vyondys 53 is designed to bind to exon 53 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 53 skipping.[1] These patients represent up to 10% of all patients with DMD.[5] This genetic manipulation intends to restore the reading frame of the resulting mRNA. The result would be production of a shortened, but partially functional dystrophin protein as seen in less severe forms of muscular dystrophy (e.g., Becker muscular dystrophy). Of note, the reading frame of certain deletions (e.g., exon 52 deletions) can be restored by skipping either exon 51 or exon 53.[6] Approximately 8% of mutations are amenable to skipping exon 53 with Vyondys 53 but are not amenable to skipping of exon 51.

Guidelines

There are guidelines for the diagnosis and management of DMD available from the DMD Care Considerations Working Group (2018).[4] Genetic testing for a DMD mutation in a blood sample is always required. By fully characterizing the mutation, the predicted effect on the reading frame can be identified, which is the major determinant of phenotype and will determine eligibility for mutation-specific clinical trials. In patients with no mutation identified but with signs/symptoms of DMD, a muscle biopsy is clinically indicated. Glucocorticoids slow decline in muscle strength and function in DMD. Use of corticosteroids reduces the risk of scoliosis and stabilizes pulmonary function. Continued treatment after the patient loses ambulation provides a reduction in the risk of progressive scoliosis and stabilization of pulmonary function tests. Therefore, glucocorticoids should be considered for all patients with DMD. Exondys 51 (eteplirsen intravenous infusion) is mentioned as an emerging product, approved by an accelerated pathway for those with a mutation in the dystrophin gene amenable to exon 51 skipping. However, these guidelines do not specifically address exon 53 skipping or mention Vyondys 53.

POLICY STATEMENT

The prescribing information for Vyondys 53 states that approval is based on dystrophin production in a limited number of patients (n = 25) with DMD, but approval may be contingent upon a confirmatory trial. Due to inadequate clinical efficacy data, **approval is not recommended** for Vyondys 53.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vyondys 53 is not recommended in the following situations:

3. **Duchenne Muscular Dystrophy (DMD).** Approval is not recommended due to the unclear clinical benefit of Vyondys 53 and lack of clinical efficacy data. Shortcomings of the clinical data with Vyondys 53 are numerous. In the pivotal trial, a minimal increase in dystrophin level was noted, but has not been correlated with a clinical benefit. Available data from the pivotal study did not provide any information to determine if Vyondys 53 provides a benefit regarding cardiac and respiratory complications which contribute greatly to morbidity and mortality in patients with DMD. Further, there are concerns of renal toxicity with utilization of Vyondys 53, and available data do not support optimal timing for initiation or discontinuation of Vyondys 53. Vyondys 53 has not been proven to alter or delay disease progression in patients with DMD amenable to exon 53 skipping. A systematic review and meta-analysis of other exon skipping therapies (i.e., Exondys 51, drisapersen) does not show benefit of these therapies for DMD.[7] The prescribing information notes that continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.[1] FDA has required a post-marketing confirmatory trial to verify the clinical efficacy of Vyondys 53.[10] This double-blind, placebo-controlled, Phase III study is estimated to be completed by October 2025.

   The efficacy of Vyondys 53 was evaluated in one published, open-label study in patients with DMD that is amenable to exon 53 skipping.[1,8] Dystrophin protein at Week 48 and 6-minute walk test (6MWT) results at Week 144 were the primary clinical endpoints. Among the patients who received Vyondys 53 in Part 2 of the study (n = 25) the normal dystrophin protein increased from baseline (0.10%) through Week 48 (1.02%; $P < 0.001$). In individual patient biopsies at Week 48, the dystrophin level ranged from 0.09% to 4.3%, with a mean per-patient 16.0-fold increase in dystrophin. At Week 48, the mean level of exon 53 skipping increased to 18.6% (SD, 13.2%; range, 2.6% to 48.0%) vs. 2.6% (SD, 4.1%; range, 0.0 to 14.7%) at baseline. The percent dystrophin-positive fibers scoring increased from 1.4% (SD, 2.4%; range, 0.06% to 9.8%) at baseline to 10.5% (SD, 10.1%; range, 0.9% to 32.6%) [$P < 0.001$) at Week 48. There was a mean per-patient 13.5-fold increase in percent dystrophin-positive fibers from baseline through Week 48. 6MWT declined by 26.1 m, 64.6 m, and 99.0 m at Weeks 48, 96, and 144, respectively.[9] When compared with a natural history external control, there was numerically less decline from baseline with Vyondys 53 (-99 m with Vyondys vs. -181 m in the natural cohort); however, this difference did not reach statistical significance. Two patients in the Vyondys 53 group lost ambulation. The percent predicted forced vital capacity declined by 8.4% (92.7% at baseline to 83.8% at Week 144).

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Natpara Prior Authorization Policy
- Natpara® (parathyroid hormone subcutaneous injection – Shire-NPS/Takeda)

REVIEW DATE: 04/19/2023

OVERVIEW

Natpara, a replica of the endogenous parathyroid hormone, is indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with **hypoparathyroidism**.[1]

Limitations of Use: due to the potential risk of osteosarcoma, Natpara is recommended only for patients who cannot be well-controlled on calcium supplements and active forms of vitamin D alone. Natpara was not studied in patients with hypoparathyroidism caused by calcium-sensing receptor mutations; and Natpara was not studied in patients with acute post-surgical hypoparathyroidism.

Before initiating and during therapy with Natpara, 25-hydroxyvitamin D stores should be sufficient.[1] In addition, before initiating Natpara, serum calcium concentration should be > 7.5 mg/dL In the pivotal study, a responder to Natpara therapy was defined as an individual who had: ≥ 50% reduction from baseline in the dose of active vitamin D, ≥ 50% reduction from baseline in the dose of oral calcium supplementation, and an albumin-corrected total serum calcium concentration between 7.5 mg/dL and 10.6 mg/dL.

Natpara has a Boxed Warning about the risk of osteosarcoma.[1] Parathyroid hormone has been shown to increase the incidence of osteosarcoma in male and female rats; the risk was dependent on dose and treatment duration. A risk to humans could not be excluded. Natpara is available only through a restricted Risk Evaluation and Mitigation Strategy (REMS) program; only certified healthcare providers can prescribe and only certified pharmacies can dispense Natpara.

Note: Natpara continues to be unavailable except for select patients through a Special Use Program. On October 4, 2022, the manufacturer (Takeda) released a statement that it will discontinue manufacturing Natpara globally at the end of 2024 due to unresolved supply issues.[2] Takeda will not re-commercialized Natpara in the US (or globally). Beyond 2024, Takeda intends to supply available doses until inventory is depleted or expired.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Natpara. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Natpara as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Natpara to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Natpara is recommended in those who meet the following criteria:

FDA-Approved Indication

61. Chronic Hypoparathyroidism. Approve for 1 year if the patient meets ONE of the following conditions (A or B):

A) Initial Therapy. Approve if the patient meets ALL of the following criteria (i, ii, iii, and iv):

i. Patient cannot be well-controlled on calcium supplements and active forms of vitamin D alone; AND

ii. Patient's 25-hydroxyvitamin D stores are sufficient (before initiating Natpara therapy) according to the prescriber; AND

iii. Patient's serum calcium concentration is > 7.5 mg/dL before initiating Natpara therapy; AND

iv. The medication is prescribed by or in consultation with an endocrinologist.

B) Patient is Currently Receiving Natpara. Approve if the patient meets ALL of the following criteria (i, ii, and iii):

i. Patient cannot be well-controlled on calcium supplements and active forms of vitamin D alone; AND

ii. Patient's 25-hydroxyvitamin D stores are sufficient (during Natpara therapy) according to the prescriber; AND

iii. Patient is responding to Natpara therapy (e.g., reduction in the patient's oral calcium dose; reduction in the patient's active vitamin D dose; maintenance of a stable albumin-corrected total serum calcium concentration), according to the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Natpara is not recommended in the following situations:

111. Acute Post-Surgical Hypoparathyroidism. Natpara was only studied in patients with chronic hypoparathyroidism.

112. Hypoparathyroidism Caused by Calcium-Sensing Receptor Mutations. Natpara was not studied in this patient population.

113. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Nephrology – Filspari Prior Authorization Policy
- Filspari™ (sparsentan tablets – Travere)

REVIEW DATE: 02/22/2023

OVERVIEW

Filspari, an endothelin and angiotensin II receptor antagonist, is indicated to reduce proteinuria in adults with **primary immunoglobulin A nephropathy** (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g.[1] This indication is approved under accelerated approval based on reduction of proteinuria. It has not been established whether Filspari slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

Filspari is contraindicated for use with renin-angiotensin-aldosterone system (RAAS) inhibitors, endothelin receptor antagonists (ERAs), or aliskiren.[1] RAAS inhibitors, ERAs, and/or aliskiren must be discontinued prior to initiation of Filspari.

Clinical Efficacy

The efficacy of Filspari is being assessed in an ongoing Phase III trial in adults with biopsy-proven IgAN, proteinuria ≥ 1.0 g/day at screening, and estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 (PROTECT, n = 404).[2] Additionally patients were receiving the maximum tolerated dose (at least one-half of the maximum labeled dose) of an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) for ≥ 12 weeks prior to study entry and had blood pressure of ≤ 150/100 mmHg (managed according to standard of care). Patients with use of immunosuppressive medications (including corticosteroids for > 2 weeks within 3 months of screening), chronic kidney disease (CKD) in addition to IgAN, or IgAN secondary to other conditions were excluded. Per study protocol, patients discontinued their ACEi or ARB 1 day prior to the start of Filspari.[2]

The primary efficacy endpoint was the change from baseline in urine protein-to-creatinine ratio (based on 24-hour urine sample) at Week 36.[2] The primary analysis was based on an interim data cutoff of August 1, 2021. At Week 36, the primary endpoint was significantly greater with Filspari vs. irbesartan in the interim analysis set (comprised of the first 281 patients randomized in the study, including 2 patients who were not treated); the geometric least squares mean percent change in UPCR from baseline was -45% vs. -15%, respectively. This resulted in a statistically significant relative reduction from baseline in UPCR for the Filspari vs. irbesartan (geometric mean ratio 0.7; 95% confidence interval [CI]: 0.6, 0.8; P < 0.0001), corresponding to a 35% relative reduction with Filspari. Supportive secondary endpoints for changes in UPCR from baseline to Week 94 and urine albumin-to-creatinine ratio (UACR) from baseline to Weeks 36 and 94, were significantly greater with Filspari. A confirmed 40% reduction in eGFR, end-stage kidney disease, or death was reported in a smaller proportion of patients treated with Filspari (3.5%) vs. irbesartan (6.4%) [P = not estimable].

Several exploratory endpoints also favored Filspari over irbesartan. At interim analysis (Week 36), the proportion of patients in the Filspari group who achieved partial proteinuria remission (< 1 g/day) was significantly higher with Filspari vs. irbesartan (55% vs. 24%, respectively) and numerically more patients in the Filspari vs. irbesartan group (11% vs. 4%, respectively) achieved complete proteinuria remission (< 0.3 g/day) at Week 36.

Guidelines

Kidney Diseases: Improving Global Outcomes (KDIGO) clinical practice guidelines for the management of glomerular diseases (2021) mention Filspari as an investigational agent.[3] Therapeutic strategies that minimize or avoid systemic glucocorticoid exposure are considered areas of priority for future research to improve the treatment and outcomes of patients with IgAN, and the PROTECT trial is mentioned. Filspari is also mentioned for children with steroid-resistant nephrotic syndrome. For children with calcineurin inhibitor-resistant steroid resistant nephrotic syndrome, consideration for entry into clinical trials evaluating novel therapies on the horizon should be strongly considered.

Following biopsy-confirmed diagnosis of IgAN, the guidelines recommend assessment of disease progression.[3] The primary focus of IgAN treatment should include multiple modalities such as RAAS blockage (maximum dose or maximum tolerated dose), blood pressure control, cardiovascular risk minimization, and adherence to lifestyle advice (i.e., dietary counseling, smoking cessation, weight control, and exercise as appropriate). RAAS blockade (with either an ACEi or ARB) is recommended regardless of hypertension if a patient has proteinuria > 0.5 g/day (500 mg/day). There are no data to suggest that dual blockade with an ACEi and ARB is superior to single blockade. In patients who remain at high risk of progressive CKD despite maximal supportive care, a 6-month course of glucocorticoid therapy should be considered.

Safety

Filspari has a Black Box Warning and Risk Evaluation and Mitigation Strategy (REMS) program around hepatotoxicity and embryo-fetal toxicity associated with Filspari.[1,4] The three objectives of the REMS are to monitor for elevations in liver enzymes in patients exposed to Filspari, ensure that patients who can become pregnant are not pregnant before initiating Filspari, and to minimize exposure in patients who may become pregnant while taking Filspari.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Filspari. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Filspari as well as the monitoring required for adverse events and long-term efficacy, approval requires Filspari to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Filspari is recommended in those who meet the following criteria:

FDA-Approved Indication

161. Primary Immunoglobulin A Nephropathy. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 9 months if the patient meets the following criteria (i, ii, iii, iv, v, vi, and vii):

- **i.** Patient is ≥ 18 years of age; AND
- **ii.** The diagnosis has been confirmed by biopsy; AND

iii. Patient is at high risk of disease progression, defined by meeting the following criteria (a and b):
- **a)** Patient meets ONE of the following [(1) or (2)]:
  - **(1)** Proteinuria > 1.0 g/day; OR
  - **(2)** Urine protein-to-creatinine ratio ≥ 1.5 g/g; AND
- **b)** Patient has received the maximum or maximally tolerated dose of ONE of the following for ≥ 12 weeks prior to starting Filspari [(1) or (2)]:
  - **(1)** Angiotensin converting enzyme inhibitor; OR
  - **(2)** Angiotensin receptor blocker; AND

iv. Patient has received ≥ 3 months of optimized supportive care, including blood pressure management, lifestyle modification, and cardiovascular risk modification, according to the prescriber; AND

v. Patient has an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2; AND

vi. The medication will not be used in combination with any renin-angiotensin-aldosterone antagonists (e.g., angiotensin converting enzyme inhibitors or angiotensin receptor blockers), endothelin receptor antagonists, or aliskiren; AND

Note: Examples of angiotensin converting enzyme inhibitors include but are not limited to lisinopril, fosinopril, enalapril, benazepril. Examples of angiotensin receptor blockers include but are not limited to irbesartan, losartan, candesartan, valsartan.

vii. The medication is prescribed by or on consultation with a nephrologist.

B) Patient is Currently Receiving Filspari. Approve for 1 year if the patient meets the following criteria (i, ii, iii, iv, v, and vi):

i. Patient is ≥ 18 years of age; AND

ii. The diagnosis has been confirmed by biopsy; AND

iii. Patient has had a response to Filspari, according to the prescriber; AND

Note: Examples of a response are a reduction in urine protein-to-creatinine ratio from baseline, reduction in proteinuria from baseline.

iv. Patient has an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2; AND

v. The medication is not being used in combination with any renin-angiotensin-aldosterone antagonists (e.g., angiotensin converting enzyme inhibitors or angiotensin receptor blockers), endothelin receptor antagonists, or aliskiren; AND

Note: Examples of angiotensin converting enzyme inhibitors include but are not limited to lisinopril, fosinopril, enalapril, benazepril. Examples of angiotensin receptor blockers include but are not limited to irbesartan, losartan, candesartan, valsartan.

vi. The medication is prescribed by or on consultation with a nephrologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Filspari is not recommended in the following situations:

243. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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762. Kidney Diseases: Improving Global Outcomes (KDIGO) 2021 clinical practice guidelines for the management of glomerular diseases. *Kidney Int.* 2021;100:S1-S276. Available at: https://www.kidney-international.org/action/showPdf?pii=S0085-2538%2821%2900562-7. Accessed on February 20, 2023.
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PRIOR AUTHORIZATION POLICY

POLICY: Nephrology – Jesduvroq Prior Authorization Policy
- Jesduvroq® (daprodustat tablets – GlaxoSmithKline)

REVIEW DATE: 09/27/2023

OVERVIEW

Jesduvroq, a hypoxia-inducible factor prolyl hydroxylase inhibitor, is indicated for the treatment of anemia due to chronic kidney disease (CKD) in adults who have been receiving dialysis for at least 4 months.[1]

Jesduvroq has not been shown to improve quality of life, fatigue, or patient well-being.[1] Jesduvroq is not indicated for the following uses:
- As a substitute for red blood cell (RBC) transfusions in those who require immediate correction of anemia.
- For the treatment of anemia of CKD in patients who are not on dialysis.

Also, it is recommended to evaluate the iron status in patients before and during Jesduvroq therapy.[1] Administer supplemental iron therapy when serum ferritin is < 100 mcg/mL or when serum transferrin saturation is < 20%. The majority of patients with CKD will require supplemental iron during the course of therapy. Do not target a hemoglobin level higher than 11.0 g/dL. If the hemoglobin level exceeds 12.0 g/dL, interrupt treatment with Jesduvroq. When the hemoglobin level is within the target range, treatment may be restarted at a lower level. Treatment with Jesduvroq should not be continued beyond 24 weeks of therapy if a clinically meaningful increase in hemoglobin level is not achieved.

Guidelines

Jesduvroq is not addressed in guidelines. The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for anemia in CKD (2012) state that for adults with CKD 5D (kidney failure; on dialysis), erythropoiesis-stimulating agent (ESA) therapy should be used to avoid having the hemoglobin concentration fall below 9.0 g/dL by initiating ESAs when the hemoglobin level is between 9.0 and 10.0 g/dL.[2] The KDIGO guidelines state that individualization of therapy is reasonable as some patients may have improvement in quality of life at higher hemoglobin levels and ESA therapy may be started for hemoglobin levels above 10.0 g/dL. In general, ESAs should not be used to maintain hemoglobin levels above 11.5 g/dL for adult patients with CKD. Individualization of therapy will be necessary as some patients may have improvements in quality of life at a hemoglobin concentration above 11.5 g/dL and will be able to handle the risks. In adults, ESAs should not be given to intentionally increase hemoglobin levels above 13.0 g/dL.

Safety

Jesduvroq has a Boxed Warning regarding an increased risk of death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access.[1] Targeting a hemoglobin level greater than 11.0 g/dL is expected to further increase the risk of death and arterial venous thrombotic events, as occurs with ESAs, which also increase erythropoietin levels. No trial has identified a hemoglobin target level, dose of Jesduvroq, or dosing strategy that does not increase these risks. Use the lowest dose of Jesduvroq sufficient to reduce the need for RBC transfusions. If the hemoglobin level is > 12 g/dL, interrupt treatment with Jesduvroq. When the hemoglobin level is within the target range, treatment may be restarted.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Jesduvroq. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Jesduvroq, as well as the monitoring required for adverse events and long-term efficacy, approval requires Jesduvroq to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Jesduvroq is recommended in those who meet the following criteria:

FDA-Approved Indication

9. Anemia in a Patient with Chronic Kidney Disease who is on Dialysis. Approve for the duration noted below if the patient meets one of the following (A or B):

E) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, iv, and v):

v. Patient is ≥ 18 years of age; AND

vi. Patient has been receiving dialysis for at least 4 consecutive months; AND

vii. Patient meets ONE of the following (a or b):

e) Patient meets BOTH of the following (1 and 2):

(1) Patient is currently receiving an erythropoiesis-stimulating agent AND transitioning to Jesduvroq; AND
Note: Examples of erythropoiesis-stimulating agents include epoetin alfa products (e.g., Epogen, Procrit, or Retacrit intravenous or subcutaneous injection), Aranesp (darbepoetin alfa intravenous or subcutaneous injection), or Mircera (methoxy polyethylene glycol-epoetin beta intravenous or subcutaneous injection).

(2) Patient has a hemoglobin level ≤ 12.0 g/dL; OR

f) Patient meets BOTH of the following (1 and 2):

(1) Patient is NOT currently receiving an erythropoiesis-stimulating agent; AND
Note: Examples of erythropoiesis-stimulating agents include epoetin alfa products (e.g., Epogen, Procrit, or Retacrit intravenous or subcutaneous injection), Aranesp (darbepoetin alfa intravenous or subcutaneous injection), or Mircera (methoxy polyethylene glycol-epoetin beta intravenous or subcutaneous injection).

(2) Patient has a baseline (prior to initiation of Jesduvroq) hemoglobin level < 11 g/dL; AND

viii. Patient meets one of the following (a or b):

a) Patient is currently receiving iron therapy; OR

b) According to the prescriber, patient has adequate iron stores; AND

ix. The medication is prescribed by or in consultation with a nephrologist; OR

F) Patient is Continuing Therapy with Jesduvroq. Approve for 1 year if the patient meets the following (i, ii, iii, iv, v, and vi):
Note: For a patient who has not received 6 months (24 weeks) of therapy or who is restarting therapy, refer to Initial Therapy criteria above.

i. Patient is ≥ 18 years of age; AND

ii. Patient has been receiving dialysis for at least 4 consecutive months; AND

iii. Patient has a hemoglobin level ≤ 12.0 g/dL; AND

iv. Patient meets ONE of the following (a or b):

a) Patient is currently receiving iron therapy; OR
b) According to the prescriber, patient has adequate iron stores; AND

v. The medication is prescribed by or in consultation with a nephrologist; AND

vi. According to the prescriber, patient has experienced a response to therapy.
Note: Examples of a response include an increase or stabilization in hemoglobin levels or a reduction or absence in red blood cell transfusions.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Jesduvroq is not recommended in the following situations:

36. **Anemia in a Patient with Chronic Kidney Disease who is NOT on Dialysis.** Jesduvroq is not indicated for use for the treatment of anemia of chronic kidney disease in patients who are not on dialysis.[1] The safety of Jesduvroq has not been established for the treatment of anemia due to CKD. In a large cardiovascular outcomes trial in adults with anemia of CKD who were not on dialysis (ASCEND-ND), an increased risk of cardiovascular mortality, stroke, thromboembolism, serious acute kidney injury, hospitalization for heart failure, and serious gastrointestinal erosions was observed in patients treated with Jesduvroq compared with erythropoietin-stimulating agent therapy.[3]

37. **Anemia Associated with Cancer.** Jesduvroq is not indicated for this use.[1]

38. **Active Malignancy.** Jesduvroq has not been studied and is not recommended in patients with active malignancies. Increased hypoxia inducible factor-1 levels may be associated with unfavorable effects on cancer growth.

39. **Anemia due to Acute Blood Loss.** Use of Jesduvroq is not appropriate in these types of situations. Jesduvroq is not indicated for use as a substitute for transfusion in patients requiring immediate correction of anemia.

40. **Concurrent Use with Erythropoiesis-Stimulating Agents.** Concomitant use is not recommended.
Note: Examples of erythropoiesis-stimulating agents include epoetin alfa products (Procrit, Epogen, Retacrit intravenous or subcutaneous injection), Aranesp (darbepoetin alfa intravenous or subcutaneous injection), and Mircera (methyoxy polyethylene glycol-epoetin beta intravenous or subcutaneous injection).

41. **To Enhance Athletic Performance.** Jesduvroq is not recommended for approval because this indication is excluded from coverage in a typical pharmacy benefit.

42. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

764. Jesduvroq® tablets [prescribing information]. GlaxoSmithKline: Research Triangle Park, NC: February 2023.
765. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney Int. 2012;2(Suppl):279-335.
766. Singh AJ, Carroll K, McMurray JJV, et al, for the ASCEND-ND Study Group. Daprodustat for the treatment of anemia in patients not undergoing dialysis. N Engl J Med. 2021;385(25):2313-2324.

PRIOR AUTHORIZATION POLICY

POLICY: Nephrology – Tarpeyo Prior Authorization Policy
- Tarpeyo™ (budesonide delayed-release capsules – Calliditas)

REVIEW DATE: 01/11/2023

OVERVIEW

Tarpeyo, a corticosteroid, is indicated to reduce proteinuria in adults with **primary immunoglobulin A nephropathy (IgAN)** at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥ 1.5 g/g.[1] This indication is approved under accelerated approval based on a reduction in proteinuria. It has not been established whether Tarpeyo slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

The recommended dose is 16 mg orally once daily (QD) at least 1 hour before a meal for 9 months.[1] When discontinuing therapy, the dose is reduced to 8 mg QD for the last 2 weeks of therapy. Safety and efficacy of treatment with subsequent courses of Tarpeyo have not been established.

Clinical Efficacy

The efficacy of Tarpeyo was evaluated in one pivotal, 9-month trial in patients ≥ 18 years of age with IgAN.[1] Eligible patients had biopsy-proven IgAN, proteinuria (defined as either ≥ 1 g/day or UPCR ≥ 0.8 g/g despite optimized supportive care), and estimated glomerular filtration rate (eGFR) ≥ 35 mL/min/1.73 m^2 and ≤ 90 mL/min/1.73 m^2.[2] Optimized supportive care required that patients receive the maximum tolerated or maximum allowed dose of an angiotensin-converting enzyme inhibitor and/or angiotensin II type I receptor blocker for ≥ 3 months prior to randomization and continued throughout the trial. Tarpeyo resulted in statistically greater reduction in UPCR and less eGFR decline relative to placebo after 9 months of treatment. As part of a prespecified analysis, it was observed that in the subgroup of patients who entered the trial with baseline UPCR ≥ 1.5 g/g, the eGFR benefit was greater in the Tarpeyo-treated patients vs. the overall population, further supporting the approved indication.

Guidelines

Tarpeyo is recognized as new therapy "in development" for high-risk IgAN patients by the Kidney Diseases Improving Global Outcomes (KDIGO) guidelines for the management of glomerular diseases (2021).[3] According to the guidelines, a number of new therapies for high-risk IgAN patients are being evaluated that may augment the supportive care approach or more specific approaches (e.g., Tarpeyo, various complement inhibitors, and therapies targeting B-cell development).

Following biopsy-confirmed diagnosis of IgAN, the guidelines recommend assessment of disease progression.[3] The primary focus of IgAN treatment should include multiple modalities such as renin angiotensin system blockage (maximum dose or maximum tolerated dose), blood pressure control, cardiovascular risk minimization, and adherence to lifestyle advice (i.e., dietary counseling, smoking cessation, weight control, and exercise as appropriate). When proteinuria remains > 0.75 to 1.0 g/day despite ≥ 90 days of optimized supportive care, the patient has a high risk of progressive loss of kidney function and may be considered for a 6-month course of steroid therapy (recently cited trials include prednisone or methylprednisolone), or preferably the opportunity to take part in a clinical trial.[4] Guidelines point out that the clinical benefit of steroids in IgAN is not established, and should be used with extreme caution or avoided in patients with eGFR < 30 mL/min/1.73 m^2, diabetes, obesity (body mass index > 30

kg/m^2), latent infections (e.g., tuberculosis, viral hepatitis), secondary disease (e.g., cirrhosis), active peptic ulceration, uncontrolled psychiatric illness, and severe osteoporosis. There are no data to support the efficacy or reduced toxicity of alternate day steroid regimens or dose-reduced protocols.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tarpeyo. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tarpeyo as well as the monitoring required for adverse events and long-term efficacy, approval requires Tarpeyo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tarpeyo is recommended in those who meet the following criteria:

FDA-Approved Indication

162. Primary Immunoglobulin A Nephropathy. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 10 months if the patient meets the following criteria (i, ii, iii, iv, v, vi, and vii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** The diagnosis has been confirmed by biopsy; AND
- **iii.** Patient is at high risk of disease progression, defined by meeting the following criteria (a and b):
  - **a)** Patient meets ONE of the following [(1) or (2)]:
    - **(1)** Proteinuria > 0.75 g/day; OR
    - **(2)** Urine protein-to-creatinine ratio ≥ 1.5 g/g; AND
  - **b)** Patient has been receiving the maximum or maximally tolerated dose of ONE of the following for ≥ 90 days [(1) or (2)]:
    - **(1)** Angiotensin converting enzyme inhibitor; OR
    - **(2)** Angiotensin receptor blocker; AND
- **iv.** According to the prescriber, the patient has received ≥ 90 days of optimized supportive care, including blood pressure management, lifestyle modification, and cardiovascular risk modification; AND
- **v.** Patient has an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2; AND
- **vi.** Patient has not previously been treated with Tarpeyo; AND
  Note: For a patient currently receiving Tarpeyo, review using Criterion 1B.
- **vii.** The medication is prescribed by or on consultation with a nephrologist.

C) Patient is Currently Receiving Tarpeyo. Approve for up to 10 months (total) if the patient meets the following criteria (i, ii, iii, iv, v, and vi):
Note: Approval is not to exceed 10 consecutive months; for example if a patient has received 3 consecutive months approve 7 months to complete 10 consecutive months of therapy.
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** The diagnosis has been confirmed by biopsy; AND

iii. Patient has been receiving the maximum or maximally tolerated dose of ONE of the following for ≥ 90 days (a or b):
  a) Angiotensin converting enzyme inhibitor; OR
  b) Angiotensin receptor blocker; AND
iv. According to the prescriber, the patient has received ≥ 90 days of optimized supportive care, including blood pressure management, lifestyle modification, and cardiovascular risk modification; AND
v. Patient has an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2; AND
vi. The medication is prescribed by or on consultation with a nephrologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tarpeyo is not recommended in the following situations:

244. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

767. Tarpeyo™ capsules [prescribing information]. Stockholm, Sweden: Calliditas; December 2021.
768. Barratt J, Lafayette R, Kristensen J, et al; for the NefIgArd Trial Investigators. Results from part A of the Multicenter, double-blind, randomized, placebo-controlled NefIgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy. *Kidney International.* 2022 Oct 19 [Epub ahead of print].
769. KDIGO 2021 clinical practice guidelines for the management of glomerular diseases. *Kidney International.* 2021;100:S1-S276. Available at: https://www.kidney-international.org/action/showPdf?pii=S0085-2538%2821%2900562-7. Accessed on: January 10, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Nephrology – Xphozah Prior Authorization Policy
- Xphozah® (tenapanor tablets – Ardelyx)

REVIEW DATE: 11/15/2023

OVERVIEW

Xphozah, a sodium hydrogen exchanger 3 (NHE3) inhibitor, is indicated to reduce serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy.[1]

Efficacy

The efficacy of Xphozah was evaluated in three pivotal trials (PHREEDOM, BLOCK, and AMPLIFY) in patients with CKD on dialysis with hyperphosphatemia. In the PHREEDOM and BLOCK trials, patients had a serum phosphorus level of at least 6.0 mg/dL to 10.0 mg/dL.[1] In the AMPLIFY trial, patients had a serum phosphate level of 5.5 to 10 mg/dL. All patients had been on maintenance dialysis for ≥ 3 months. In all three pivotal trial, the primary endpoint, which was the difference in the mean change in serum phosphate levels in patients taking Xphozah vs. placebo was statistically significant.

Guidelines

The Kidney Disease Improving Global Outcomes (KDIGO) published a 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of CKD-mineral and bone disorder (CKD-MBD), which is a selective update of the prior CKD-MBD guideline published in 2009.[2] Xphozah is not mentioned in the guidelines. The classification of CKD in these guidelines are based upon glomerular filtration rate (G1 to G5) and albuminemia (A1 to A3); G5D represents kidney failure on dialysis. Treatment options for hyperphosphatemia include diet modification, phosphate-lowering therapy, and intensified dialysis for patients with CKD stage G5D. The following are recommendations in patients with CKD G3a to G5D. Elevated phosphate levels are suggested to be lowered toward the normal range (Grade 2C recommendation). The guideline update does not provide the reference value of normal range. Decisions about phosphate-lowering treatment is suggested to be based on progressively or persistently elevated serum phosphate (not graded). The broader term "phosphate-lowering" treatment is used instead of phosphate-binding agents since all possible approaches (i.e., phosphate binders, diet, dialysis) can be effective, which is change from the 2009 guidelines.[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Xphozah. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Xphozah as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Xphozah to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xphozah is recommended in those who meet the following criteria:

FDA-Approved Indication

163. Hyperphosphatemia in Chronic Kidney Disease. Approve for 12 months if the patient meets the following (A, B, C, D, E and F):

A) Patient is ≥ 18 years of age; AND
B) Patient has chronic kidney disease (CKD); AND
C) Patient has been on maintenance dialysis for ≥ 3 months; AND
D) Patient's serum phosphate level is ≥ 5.5 mg/dL and <10.0 mg/dL; AND
E) Patient meets one of the following (i or ii):
- **i.** Patient meets both of the following (a and b):
  - **a)** Patient has tried at least two phosphate binders; AND
    Note: Examples of phosphate binders include: sevelamer, lanthanum, ferric citrate, and sucroferric oxyhydroxide, calcium carbonate, and calcium acetate.
  - **b)** Patient had an inadequate response and/or intolerance to at least two phosphate binders; OR
- **ii.** Patient meets one of the following (a or b):
  - **a)** Patient has a contraindication to at least two phosphate binders; OR
    Note: Contraindication to phosphate binders includes bowel obstruction, iron overload, or hypercalcemia.
  - **b)** Patient meets both of the following (1 and 2):
    - **(1)** Patient has inadequate response and/or intolerance to at least one phosphate binder; AND
    - **(2)** Patient has a contraindication to at least one phosphate binder.
      Note: Contraindication to phosphate binders includes bowel obstruction, iron overload, or hypercalcemia.

F) The medication is prescribed by or on consultation with a nephrologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xphozah is not recommended in the following situations:

245. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

770. Xphozah® tablets [prescribing information]. Waltham, MA: Ardelyx; October 2023.
771. Ketteler M, Block G, Evenepoel P, et al. Diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder: synopsis of the kidney disease: improving global outcomes 2017 clinical practice guideline update. *Ann Intern Med*. 2018; 168 (6): 422-430.
772. Ketteler M, Block G, Evenepoel P, et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters. *Kidney Int*. 2017; 92(1):26.

PRIOR AUTHORIZATION POLICY

POLICY: Neurology – Aduhelm Prior Authorization Policy
- Aduhelm® (aducanumab-avwa intravenous infusion – Biogen)

REVIEW DATE: 06/07/2023

OVERVIEW
Aduhelm, an amyloid beta-directed antibody, is indicated for the **treatment of Alzheimer's disease**.[1]

This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with Aduhelm.[1] Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

Disease Overview
An estimated 6.7 million Americans ≥ 65 years of age are living with Alzheimer's dementia in 2023, with 73% of these people ≥ 75 years of age.[2] The number and proportion of older adults who have mild cognitive impairment due to Alzheimer's disease is difficult to estimate; however, a rough approximation suggests that 5 to 7 million older Americans may have mild cognitive impairment due to Alzheimer's disease. People with mild cognitive impairment due to Alzheimer's disease have biomarker evidence of brain changes due to the disease in addition to subtle problems with memory and thinking. Biomarker evidence includes abnormal levels of amyloid beta as evidenced on positron emission tomography (PET) scans and in analysis of cerebrospinal fluid, and decreased metabolism of glucose as shown on PET scans. These cognitive problems may be noticeable to the individual family members and friends, but not to others, and they do not interfere with the person's ability to carry out everyday activities. The mild changes in cognitive abilities occur when the brain can no longer compensate for the damage and death of nerve cells due to Alzheimer's disease.

Clinical Efficacy
The current Aduhelm efficacy information is insufficient to determine if the medication demonstrates any clinically meaningful benefits. In the absence of additional clinical trials, there is not enough information to support approval.

POLICY STATEMENT
Due to the lack of clinical efficacy data and safety concerns, **approval is not recommended** for Aduhelm. The current Aduhelm efficacy information is insufficient to determine if the medication demonstrates any clinically meaningful benefits; whereas, safety concerns have been demonstrated in clinical trials. In the absence of additional clinical trials, there is not enough information to support approval.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Aduhelm is not recommended in the following situations:

246. Alzheimer's Disease. Due to the lack of clinical efficacy data, approval is not recommended for Aduhelm. The prescribing information for Aduhelm states that it was approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with Aduhelm.[1] FDA has required a randomized, controlled trial evaluation post-marketing to establish efficacy of Aduhelm. Results are expected in 2030.

Two identical, Phase III, double-blind, placebo-controlled, randomized trials of high- and low-dose Aduhelm (ENGAGE and EMERGE) were conducted in patients with Alzheimer's disease (patients with confirmed presence of amyloid pathology and mild cognitive impairment or mild dementia stage of disease).[1,3,4] Approximately halfway through the two Phase III studies, a planned interim analysis met prespecified futility criteria and the trials were terminated prior to completion. A post-hoc analysis of the trials revealed that EMERGE did reach statistical significance on its primary efficacy endpoint, estimating a high-dose treatment effect corresponding to a 22% relative reduction in the Clinical Dementia Rating–Sum of Boxes (CDR-SB) score compared with placebo (P = 0.01). Efficacy was not demonstrated in the low-dose arm of EMERGE or in either treatment arm of ENGAGE. Of note, the minimum clinically important difference for the primary endpoint of CDR-SB is generally considered to be 1 to 2 on a scale from 0 to 18.[5] The 22% reduction in CDR-SB detected in the high-dose arm in EMERGE reflected an absolute difference of 0.39, which does not qualify as clinically significant.

Aduhelm can cause amyloid related imaging abnormalities-edema (ARIA-E) and amyloid related imaging abnormalities-hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis, which can be observed on magnetic resonance imaging (MRI).[1] A recent (within 1 year) MRI of the brain should be obtained prior to initiating treatment with Aduhelm. The safety of Aduhelm in patients with any pre-treatment localized superficial siderosis, ten or more brain microhemorrhages, and/or with a brain hemorrhage > 1 cm within one year of treatment initiation has not been established. Enhanced clinical vigilance for asymptomatic amyloid related imaging abnormalities (ARIA) is recommended during the first eight doses of treatment with Aduhelm, particularly during titration, because the majority of ARIA was observed during this time. MRIs of the brain should be obtained prior to the seventh infusion (first dose of 10 mg/kg) and 12th infusion (sixth dose of 10 mg/kg) of Aduhelm to evaluate for the presence of asymptomatic ARIA. If ten or more new incident microhemorrhages or greater than two focal areas of superficial siderosis (radiographic severe ARIA-H) are observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrate radiographic stabilization (i.e., no increase in size or number of ARIA-H).

247. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

773. Aduhelm™ intravenous infusion [prescribing information]. Cambridge, MA: Biogen; February 2023.
774. Alzheimer's Association. Alzheimer's disease facts and figures-2023. Available at: https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf. Accessed on June 2, 2023.
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776. Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee Meeting. Combined FDA and Applicant PCNS Drugs Advisory Committee Briefing Document. November 6, 2020. Available at: https://www.fda.gov/media/143502/download. Accessed on June 2, 2023.
777. Alexander GC, Emerson S, Kesselheim AS. Evaluation of aducanumab for Alzheimer Disease scientific evidence and regulatory review involving efficacy, safety, and futility. *JAMA*. 2021;325(17):1717-1718.

PRIOR AUTHORIZATION POLICY

POLICY: Neurology – Brineura Prior Authorization Policy
- Brineura® (cerliponase alfa intraventricular infusion – BioMarin)

REVIEW DATE: 04/12/2023

OVERVIEW

Brineura is indicated to slow the loss of ambulation in symptomatic pediatric patients ≥ 3 years of age with **late infantile neuronal ceroid lipofuscinosis type 2** (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency.[1]

Brineura is recombinant human TPP1 produced using recombinant DNA technology.[1] The recommended dose of Brineura is 300 mg administered once every other week (QOW) via intracerebroventricular (ICV) infusion. Following Brineura administration, the patient must also receive an infusion of intraventricular electrolytes. The drug is administered into the cerebral spinal fluid via a surgically implanted reservoir and catheter. It should only be administered by or under the direction of a physician who is knowledgeable in ICV administration.

Disease Overview

CLN2 disease is an ultra-rare neurodegenerative disorder that is part of a group of neuronal ceroid lipofuscinoses (NCLs) sometimes referred to as Batten disease.[2] NCL diseases are a heterogeneous group of incurable neurodegenerative lysosomal storage diseases. They manifest as early impairment of vision, loss of cognitive and motor functions, seizures, and premature death. To date, 13 genetic mutations have been discovered to cause the multiple variations of the disease (e.g., CLN1, CLN2, CLN3 etc.). Classic late infantile NCL disease is caused by a mutation in the CLN2 gene, which encodes for lysosomal TPP1. Without TPP1, lysosomal storage materials accumulate, contributing to the progressive and persistent neurodegeneration.[2] In CLN2 disease, symptom onset is typically between 2 and 4 years of age, and lifespan is around 6 to 14 years. Other NCLs result in deficiencies in enzymes other than TPP1. As Brineura is human recombinant TPP1, its efficacy is specific to CLN2 disease.

Guidelines

Recently published expert recommendations state that patients with a suspected NCL disorder require NCL-specific diagnostic testing.[3-5] Patients require assessment by a metabolic specialist/geneticist, an NCL specialist, or a pediatric neurologist with experience in diagnosing NCL disorders. Expert recommendation from 2016 stated that the recommended gold standard for laboratory diagnosis from experts was the demonstration of deficient TPP1 enzyme activity (in leukocytes, fibroblasts, or dried blood spots) and the identification of pathogenic variants in both alleles of the TPP1/CLN2 gene for confirmation of CLN2 disease.[4] When it is not possible to perform both analyses, either demonstration of deficient TPP1 enzyme activity in leukocytes or fibroblasts, or detection of two pathogenic variants in the CLN is diagnostic for CLN2 disease.[4] The 2021 guidelines established that the diagnosis of CLN2 can be confirmed by low levels of TPP1 enzyme activity and should be double confirmed by detecting two disease-causing mutations in the CLN2 gene.[5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Brineura. All approvals are provided for the duration noted below. Because of the of the specialized skills required for evaluation and diagnosis of patients treated with Brineura as well as the monitoring required for adverse events and long-term efficacy, approval requires Brineura to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Brineura is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Late Infantile Neuronal Ceroid Lipofuscinosis Type 2 (CLN2).** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   - **B)** Patient is ≥ 3 years of age; AND
   - **C)** Patient has two pathogenic mutations in the CLN2 gene as confirmed by genetic testing; AND
   - **D)** Patient has had a test which confirms reduced activity of tripeptidyl peptidase 1 (TPP1); AND
   - **E)** Brineura is prescribed by or in consultation with a metabolic specialist, geneticist, pediatric neurologist, or a physician specializing in the treatment of neuronal ceroid lipofuscinoses (NCLs).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Brineura is not recommended in the following situations:

1. **Neuronal Ceroid Lipofuscinoses (NCLs) other than late infantile ceroid lipofuscinosis type 2 (CLN2) [e.g., CLN1, CLN3, CLN10, CLN13, and others].** Brineura has not been studied for NCLs involving mutations in genes other than CLN2.[1]

2. Coverage is not recommended for circumstances *not* listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Neurology – Daybue Prior Authorization Policy
- Daybue™ (trofinetide oral solution – Acadia)

REVIEW DATE: 04/12/2023; selected revision 05/24/2023

OVERVIEW

Daybue is indicated for the treatment of Rett syndrome in adults and pediatric patients ≥ 2 years of age.[1]

Disease Overview

Rett syndrome is a neurodevelopmental disorder characterized by typical early growth and development followed by a slowing of development, loss of functional use of the hands, distinctive hand movements, slowed brain and head growth, problems with walking, seizures, and intellectual disability.[2] The course of Rett syndrome, including the age of onset and the severity of symptoms, varies from child to child. However, symptoms of Rett syndrome usually appear in children between 6 to 18 months as they begin to miss developmental milestones or lose abilities they had gained.[3] Rett syndrome occurs worldwide in 1 of every 10,000 to 15,000 female births and is even rarer in males. Rett syndrome is estimated to affect all racial and ethnic groups worldwide.[2] Nearly all cases of Rett syndrome are caused by a mutation in the methyl CpG binding protein 2 (MECP2) gene. The MECP2 gene contains instructions for the synthesis of a protein called methyl cytosine binding protein 2 (MeCP2), which is needed for brain development and acts as a biochemical switch that can increase or decrease gene expression.

Typical, or classic, Rett syndrome is defined by the presence of the characteristic disease progression of Rett syndrome, a period of regression followed by recovery or stabilization.[4,5] The diagnosis of classic/typical Rett syndrome requires all main diagnostic criteria and none of the exclusion criteria. The main Rett syndrome diagnostic criteria are: 1) partial or complete loss of acquired purposeful hand skills; 2) partial or complete loss of acquired spoken language; 3) gait abnormalities, i.e., impaired (dyspraxic) or absence of ability; and 4) stereotypic hand movements, such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms. The exclusion criteria for classic/typical Rett syndrome are: 1) brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems; and 2) grossly abnormal psychomotor development in first 6 months of life. Additionally, clinicians have also identified individuals that display some, but not all, of the features of typical Rett syndrome.[4] These individuals are described to have atypical, or variant, Rett syndrome. Atypical Rett syndrome is defined by the presence of a period of regression followed by recovery or stabilization, as well as at least 2 of the main 4 criteria for typical Rett syndrome and at least 5 of the 11 supporting criteria: breathing disturbances when awake; bruxism when awake; impaired sleep pattern; abnormal muscle tone; peripheral vasomotor disturbances; scoliosis/kyphosis; growth retardation; small cold hands and feet; inappropriate laughing/screaming spells; diminished response to pain; and intense eye communication, use of eye pointing.[5]

Because *MECP2* mutations are now identified in some individuals prior to any clear evidence of regression, the diagnosis of "possible" Rett syndrome should be given to those individuals < 3 years of age who have not lost any skills but otherwise have clinical features suggestive of Rett syndrome.[5] These individuals should be reassessed every 6 to 12 months for evidence of regression. If regression manifests, the diagnosis should then be changed to definite Rett syndrome. However, if the child does not show any evidence of regression by 5 years of age, the diagnosis of Rett syndrome should be questioned.

Clinical Efficacy

The current Daybue efficacy information is insufficient to determine if the medication demonstrates any clinically meaningful benefits.[6-8] In the absence of additional clinical trials, there is not enough information to support approval. The efficacy of Daybue was evaluated in one pivotal trial called LAVENDER that assessed Daybue in female patients with Rett syndrome.[6,7] Confirmatory evidence of efficacy was provided by RETT-002, a non-pivotal, dose-ranging trial that evaluated Daybue in female patients with Rett syndrome.[8] Evidence for effectiveness in patients 2 to 4 years of age with Rett syndrome was provided by a bridging pharmacokinetic study, DAFFODIL.[7] For each of these studies, patients were enrolled if they had a diagnosis of typical Rett syndrome, according to the Rett syndrome diagnostic criteria, with a documented disease-causing mutation in the MECP2 gene, and were post-regression status for ≥ 6 months at screening (i.e., no loss or degradation in ambulation, hand function, speech, nonverbal communicative or social skills).[6-8]

POLICY STATEMENT

Due to the lack of clinical efficacy data and safety concerns, **approval is not recommended** for Daybue. The current Daybue efficacy information is insufficient to determine if the medication demonstrates any clinically meaningful benefits. In the absence of additional clinical trials, there is not enough information to support approval.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Daybue is not recommended in the following situations:

248. Rett Syndrome. The efficacy of Daybue was evaluated in one pivotal trial called LAVENDER that assessed Daybue in female patients with Rett syndrome.[6,7] A non-pivotal, dose-ranging trial, RETT-002, also evaluated Daybue in female patients with Rett syndrome.[8] Evidence for use in patients 2 to 4 years of age with Rett syndrome was provided by a bridging pharmacokinetic study, DAFFODIL.[7] For each of these studies, patients were enrolled if they had a diagnosis of typical Rett syndrome, according to the Rett syndrome diagnostic criteria, with a documented disease-causing mutation in the MECP2 gene, and were post-regression status for ≥ 6 months at screening (i.e., no loss or degradation in ambulation, hand function, speech, nonverbal communicative or social skills).[6-8] After 12 weeks, LAVENDER demonstrated marginal efficacy on the subjective co-primary efficacy endpoints of the Rett Syndrome Behaviour Questionnaire (RSBQ) [the scale ranges from 0 to 90] and the Clinical Global Impression-Improvement (CGI-I) score (scale ranges from 0 to 7).[6,7]

249. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Neurology – Gene Therapy – Skysona Prior Authorization Policy
- Skysona® (elivaldogene autotemcel intravenous infusion – Bluebird Bio)

REVIEW DATE: 11/15/2023

OVERVIEW

Skysona, an autologous hematopoietic stem cell-based gene therapy, is indicated to slow the progression of neurologic dysfunction in boys 4 to 17 years of age with early, active **cerebral adrenoleukodystrophy**.[1] Early, active cerebral adrenoleukodystrophy refers to asymptomatic or mildly symptomatic (neurologic function score [NFS] ≤ 1) boys who have gadolinium enhancement on brain magnetic resonance imaging (MRI) and Loes scores of 0.5 to 9 points.[1] This indication was approved under accelerated approval based on 24-month Major Functional Disability (MFD)-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Skysona is given as a single dose by intravenous infusion; the minimum recommended dose is 5.0×10^6 $CD34^+$ cells/kg.

Disease Overview

Cerebral adrenoleukodystrophy is a rare, neurodegenerative X-linked genetic disease in young boys that mainly affects the nervous system and adrenal glands.[2-4] The estimated incidence of adrenoleukodystrophy is 1:20,000 to 1:30,000 males. It is caused by a defect in the adenosine triphosphate-binding cassette, subfamily D, member 1 (*ABCD1*) gene. Very long chain fatty acids accumulate, which causes inflammation in and damage to the brain; other tissue types are also impacted. Around 40% of patients with adrenoleukodystrophy will develop cerebral adrenoleukodystrophy which is associated with rapid, progressive cerebral demyelination which usually occurs when patients are 3 to 12 years of age. Early stages of cerebral adrenoleukodystrophy are clinically asymptomatic and are only detected by performing an MRI of the brain. Irreversible, devastating neurologic decline can result which include MFDs such as loss of communication, cortical blindness, dependence on tube feeding, total incontinence, use of a wheelchair for ambulation, or complete loss of voluntary movement. As the disease progresses, patients often develop profound disability. If an allogeneic hematopoietic stem cell transplantation (HSCT) is not performed, almost one-half of impacted patients will likely die within 5 years of symptom onset.

Clinical Efficacy

The efficacy of Skysona was assessed in two 24-month, open-label, single arm, single-dose, multicenter, multinational pivotal trials involving male patients ≤ 17 years of age with early, active cerebral adrenoleukodystrophy as defined by its FDA-approved indication.[1,5,6] STARBEAM (ALD-102) [published data in 17 patients] {n = 32} was a Phase II/III investigation which is completed and involved patients who did not have a matched sibling donor for allogeneic HSCT. Study 2 (ALD-104) [unpublished] {n = 35} is an ongoing study and patients with a matched sibling donor for allogeneic HSCT could participate. Skysona was compared with a natural history population, as well as patients who underwent allogeneic HSCT. Patients in both studies could enroll in a long-term follow-up study (LTF-304). It should be noted that patients involved in these two studies had elevated very long chain fatty acid levels and confirmed mutations in the *ABCD1* gene. In the published STARBEAM study, at time of the interim analysis (April 2017), a total of 17 boys had received Skysona with a median follow-up of 29.4 months (range 21.6 to 42.0 months). In total, 88% of patients (n = 15/17) who received Skysona were alive and free of an MFD; all maintained an NFS score of 0 to 1.[5] In the symptomatic Skysona subpopulation (n = 11), slower progression to MFD or death (MFD-free survival) from time of symptom onset (first NFS ≥ 1) was observed compared with a similar natural history population (n = 7).[1] Data involving the entire efficacy population (n = 61) analyzed

overall survival compared to early, active allogeneic HSCT subpopulations by various donor type (human leukocyte antigen [HLA]-matched allogeneic HSCT subpopulation [n = 34] and HLA-mismatched allogeneic HSCT subpopulation [n = 17]). A reduced overall survival was noted in the first 9 months after treatment among the subpopulation who received allogeneic HSCT from an HLA-mismatched donor compared with Skysona, as well as the group who received an allogeneic HSCT from an HLA-matched donor (results presented graphically). The earlier mortality in the HLA-mismatched allogeneic HSCT subpopulation was mainly due to allogeneic HSCT-related toxicities.

Guidelines

Skysona has not been addressed in guidelines post FDA-approval. In September 2022, international recommendations for the diagnosis and management of patients with adrenoleukodystrophy (a consensus-based approach) were published.[7] It was noted that allogeneic HSCT is the standard treatment for cerebral adrenoleukodystrophy and can halt progression. Genetically transduced autologous stem cell transplantation (gene therapy [Skysona]) should be considered (if available) in boys if allogeneic donor options are poor. Outcome is poor in patients with advance disease (Loes score > 9 and/or NFS > 1). Regarding gene therapy (Skysona), it states that this therapy is not available for routine care; long-term safety data are not yet available. Treatment for boys or men with advanced disease or progressive lesions without gadolinium enhancement should only be considered after careful assessment in experienced centers.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Skysona. Approval is recommended for those who meet the Criteria for the listed indication. Because of the specialized skills required for evaluation and diagnosis of patients treated with Skysona as well as the specialized training required for administration of Skysona, approval requires Skysona to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for one dose per lifetime. The approval duration is 6 months to allow for an adequate time frame to prepare and administer one dose of therapy. For certain criteria, verification is required as noted by **[verification in claims history required]**. In the criteria for Skysona, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: males are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation. Some clients have elected Embarc Benefit Protection. For these clients, the Medical Director will coordinate with eviCore to ensure the Embarc Benefit Protection portion of the review has been completed. If the Embarc Benefit Protection portion of the review has not been completed, the Medical Director will route to Embarc@eviCore.com prior to completing the review.

Documentation: Documentation is required for use of Skysona as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, prescription claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Skysona is recommended in those who meet the following criteria:

FDA-Approved Indication

164. Cerebral Adrenoleukodystrophy. Approve a one-time (lifetime) dose if the patient meets the following (A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, R, S, T, and U).
- **A)** Patient is a male*; AND
- **B)** Patient is ≥ 4 and < 18 years of age; AND
- **C)** Patient has early, active cerebral adrenoleukodystrophy as demonstrated by meeting the following (i, ii, and iii):
  - **i.** Patient has a neurologic function score ≤ 1 **[documentation required]**; AND
  - **ii.** Patient has gadolinium enhancement on brain magnetic resonance imaging (MRI) **[documentation required]**; AND
  - **iii.** Patient has a Loes score between 0.5 and 9 **[documentation required]**; AND
- **D)** Patient has a confirmed mutation in the adenosine triphosphate binding cassette, sub family D member 1 (*ABCD1*) gene **[documentation required]**; AND
- **E)** Patient has elevated very long chain fatty acid levels according to the standard reference values of the laboratory **[documentation required]**; AND
- **F)** Patient does not have a Human Leukocyte Antigen (HLA)-matched family donor **[documentation required]**; AND
- **G)** According to the prescribing physician, the patient is able to undergo monitoring by magnetic resonance imaging; AND
- **H)** Patient does not currently have an active bacterial, viral, fungal, or parasitic infection; AND
- **I)** Patient does not have any of the following (i and ii):
  - **i.** Prior or current hematologic malignancy or myeloproliferative disorder; AND
  - **ii.** Familial cancer syndrome or a history of such in his immediate family; AND
- **J)** According to the prescribing physician, hematopoietic stem cell transplantation is appropriate for the patient; AND
- **K)** Patient has adequate hepatic function defined by meeting the following (i, ii, and iii):
  - **i.** Aspartate aminotransferase values are normal or ≤ 2.5 times the upper limit of normal **[documentation required]**; AND
  - **ii.** Alanine aminotransferase values are normal or ≤ 2.5 times the upper limit of normal **[documentation required]**; AND
  - **iii.** Total bilirubin values are normal or ≤ 3.0 mg/dL **[documentation required]**; AND
- **L)** Patient has adequate renal function as defined by meeting the following (i or ii):
  - **i.** Estimated creatinine clearance is ≥ 50 mL/min **[documentation required]**; OR
  - **ii.** Estimated glomerular filtration rate is ≥ 70 mL/minute/1.73 m^2 **[documentation required]**; AND
- **M)** According to the prescribing physician, patient does not have evidence of cardiac compromise; AND
- **N)** Prior to collection of cells for manufacturing, patient screening is negative for the following (i, ii, iii, and iv):
  - **i.** Hepatitis B virus **[documentation required]**; AND
  - **ii.** Hepatitis C virus **[documentation required]**; AND
  - **iii.** Human T-lymphotropic virus 1 and 2 **[documentation required]**; AND
  - **iv.** Human immunodeficiency virus 1 and 2 **[documentation required]**; AND
- **O)** Prior to therapy, patient does not have evidence of hematological compromise as defined by meeting the following (i, ii, iii, and iv):

i. Peripheral blood absolute neutrophil count ≥ 1,500 cells/mm^3 **[documentation required]**; AND
ii. Platelet count ≥ 100,000 cells/mm^3 **[documentation required]**; AND
iii. Hemoglobin ≥ 10 g/dL **[documentation required]**; AND
iv. Patient does not have an uncorrected bleeding disorder; AND

P) Patient meets the following (i, ii, iii, and iv):
i. Patient will undergo mobilization, apheresis, myeloablative conditioning, and lymphodepletion; AND
ii. A granulocyte-colony stimulating factor product will be used for mobilization; AND
iii. Busulfan will be used for myeloablative conditioning; AND
iv. Cyclophosphamide or fludarabine will be used for lymphodepletion; AND

Q) Patient has received or is planning to receive prophylaxis for hepatic veno-occlusive disease/hepatic sinusoidal obstruction syndrome before conditioning; AND
Note: Examples of medications used include ursodeoxycholic acid or Defitelio (defibrotide intravenous infusion).

R) The prescribing physician confirms that the patient or his partner of childbearing potential will be using an effective method of contraception from the start of mobilization through at least 6 months after administration of Skysona; AND

S) Patient has not received Skysona in the past **[verification in claims history required]**; AND
Note: Verify through claims that the patient has not previously received Skysona AND, if no claim for Skysona is present, the prescribing physician confirms that the patient has not previously received Skysona.

T) Medication is prescribed by a hematologist, a neurologist, and/or a stem cell transplant specialist physician; AND

U) The single dose is given intravenously which contains a minimum of 5.0 x 10^6 CD34+ cells/kg of body weight in which body weight is based on patient weight prior to first apheresis.

* Refer to the Policy Statement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Skysona is not recommended in the following situations:

250. Patient has a Full *ABCD1* Gene Deletion. In one patient involved in the Skysona clinical trials who had a full *ABCD1* gene deletion, disease progression occurred. The patient experienced radiologic disease progression, along with declining peripheral blood vector copy number, suggesting a loss of product efficacy which may have been immune mediated. The patient eventually underwent allogeneic HSCT for treatment. A noted limitation of use is that an immune response to Skysona may limit the persistence of descendent cells of Skysona, causing rapid loss of efficacy of Skysona in patients with full deletions of the *ABCD1* transgene.

251. Prior Hematopoietic Stem Cell Transplantation.
Note: Prescribing physician must confirm that the patient has not received a prior hematopoietic stem cell transplantation.
Prior allogeneic hematopoietic stem cell transplant was an exclusion criterion in the pivotal studies.

252. Prior Receipt of Gene Therapy. This was an exclusion criterion in the pivotal studies.

253. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Neurology – Leqembi Prior Authorization Policy
- Leqembi™ (lecanemab-irmb intravenous infusion – Eisai/Biogen)

REVIEW DATE: 01/25/2023

OVERVIEW

Leqembi, an amyloid beta-directed antibody, is indicated for the **treatment of Alzheimer's disease**.[1] Treatment with Leqembi should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials.

Disease Overview

An estimated 6.5 million Americans ≥ 65 years of age are living with Alzheimer's dementia in 2022, with 73% of these people ≥ 75 years of age.[2] The number and proportion of older adults who have mild cognitive impairment due to Alzheimer's disease is difficult to estimate; however, a rough approximation suggests that 5 million older Americans may have mild cognitive impairment due to Alzheimer's disease. People with mild cognitive impairment due to Alzheimer's disease have biomarker evidence of brain changes due to the disease in addition to subtle problems with memory and thinking. Biomarker evidence includes abnormal levels of amyloid beta as evidenced on positron emission tomography (PET) scans and in analysis of cerebrospinal fluid, and decreased metabolism of glucose as shown on PET scans. These cognitive problems may be noticeable to the individual family members and friends, but not to others, and they do not interfere with the person's ability to carry out everyday activities. The mild changes in cognitive abilities occur when the brain can no longer compensate for the damage and death of nerve cells due to Alzheimer's disease. Among those with mild cognitive impairment, about 10% to 15% develop dementia each year. Approximately one-third of people with mild cognitive impairment develop Alzheimer's dementia within 5 years.

Clinical Efficacy

The current Leqembi efficacy information is insufficient to determine if the medication demonstrates any clinically meaningful benefits. In the absence of additional clinical trials, there is not enough information to support approval.

POLICY STATEMENT

Due to safety concerns and the lack of clinically significant efficacy data, **approval is not recommended** for Leqembi. The current Leqembi efficacy information is insufficient to determine if the medication demonstrates any clinically meaningful benefits; whereas, safety concerns have been demonstrated in clinical trials. In the absence of additional clinical trials, there is not enough information to support approval.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Leqembi is not recommended in the following situations:

254. Alzheimer's Disease. Due to the lack of clinically significant efficacy data, approval is not recommended for Leqembi.

The efficacy of Leqembi for accelerated approval was evaluated in one Phase IIb randomized, double-blind, placebo-controlled, multicenter, pivotal study in patients with mild cognitive impairment due to Alzheimer's disease and mild Alzheimer's disease dementia (n = 854).[3] In the Phase IIb study, the primary endpoint, change from baseline at 12 months on Alzheimer's Disease Composite Score (ADCOMS), reached a 64% probability of being better than placebo with 25% less decline at 12 months, missing the pre-specified 80% probability threshold. However, the secondary endpoint of least squares mean change from baseline in amyloid PET Standard Uptake Value ratio (SUVr) at 18 months was significantly reduced for all dosage regimens, including Leqembi 10 mg/kg once every 2 weeks (P < 0.001 for all doses).

Additionally, one Phase III, randomized, double-blind, placebo-controlled, multicenter study (CLARITY AD) was conducted in patients with mild cognitive impairment due to Alzheimer's disease and mild Alzheimer's disease dementia (n = 1,795).[4] CLARITY AD provided the basis for traditional FDA on July 6, 2023. In CLARITY AD, the adjusted mean change from baseline at Week 78 in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score demonstrated slowing of clinical progression for Leqembi vs. placebo (treatment difference -0.45; P < 0.001 [scores range from 0 to 18, with higher scores indicating greater disease severity]). However, this slowing of progression did not achieve clinical significance.[5]

Leqembi can cause amyloid related imaging abnormalities-edema (ARIA-E) and amyloid related imaging abnormalities-hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis, which can be observed on magnetic resonance imaging (MRI).[1] A recent (within 1 year) MRI of the brain should be obtained prior to initiating treatment with Leqembi. The safety of Leqembi has not been evaluated in patients with prior cerebral hemorrhage > 1 cm in greatest diameter, more than four microhemorrhages, superficial siderosis, evidence of vasogenic edema, evidence of cerebral contusion, aneurysm, vascular malformation, infective lesions, multiple lacunar infarcts or stroke involving a major vascular territory, and severe small vessel or white matter disease. Enhanced clinical vigilance for asymptomatic amyloid related imaging abnormalities (ARIA) is recommended during the first seven doses of treatment with Leqembi, particularly during titration, because the majority of ARIA was observed during this time. MRIs of the brain should be obtained prior to the fifth infusion, seventh, and 14th infusion of Leqembi to evaluate for the presence of asymptomatic ARIA. There is no experience in patients who continued dosing through symptomatic ARIA-E or through asymptomatic, but radiographically severe, ARIA-E. There is limited experience in patients who continued dosing through asymptomatic but radiographically mild to moderate ARIA-E. There are limited data in dosing patients who experienced recurrent ARIA-E.

255. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION WITH STEP THERAPY POLICY

POLICY: Neurology – Lyrica CR Prior Authorization with Step Therapy Policy
- Lyrica® CR (pregabalin extended-release tablets – Pfizer, generic)

REVIEW DATE: 03/22/2023

OVERVIEW

Pregabalin extended-release tablets, an analog of gamma-aminobutyric acid (GABA), are indicated for the following uses:[1]
- **Neuropathic pain associated with diabetic peripheral neuropathy** (DPN), management in adults.
- **Postherpetic neuralgia** (PHN), management in adults.

The efficacy of pregabalin extended-release tablets has not been established for the management of fibromyalgia or as adjunctive therapy for adults with partial onset seizures.[1]

Gabapentin immediate-release (IR), an analog of GABA, is indicated for the following uses:[2]
- **Partial onset seizures**, with and without secondary generalization, as adjunctive therapy in adults and pediatric patients ≥ 3 years of age with epilepsy.
- **PHN**, management in adults.

Pregabalin IR capsules and oral solution are indicated for the following uses:[3]
- **Fibromyalgia**, management in adults.
- **Neuropathic pain associated with DPN**, management in adults.
- **Neuropathic pain associated with spinal cord injury**, management in adults.
- **Partial onset seizures**, as adjunctive therapy for the treatment in patients ≥ 1 month of age.
- **PHN**, management in adults.

Disease Overview

PHN is the persistence of the pain of herpes zoster > 3 months after resolution of the rash; it is relatively common, affecting 10% to 15% of those with herpes zoster.[4] Administration of antiviral agents within 72 hours of the onset of herpes zoster can reduce the intensity and duration of acute illness and can prevent PHN. Efforts to prevent herpes zoster and PHN are important because 40% to 50% of patients with PHN do not respond to any treatment.

The diabetic neuropathies are a heterogeneous group of disorders with diverse clinical manifestations.[5] The early recognition and appropriate management of neuropathy in the patient with diabetes is important. Up to 50% of DPN may be asymptomatic. Painful diabetic neuropathy affects 16% of patients with diabetes, and it is frequently unreported (12.5%) and more frequently untreated (39%).[6] If not recognized and if preventive foot care is not implemented, patients are at risk for injuries to their insensate feet.[5] Recognition and treatment of autonomic neuropathy may improve symptoms, reduce sequelae, and improve quality of life. Therapeutic strategies (pharmacologic and nonpharmacologic) for the relief of painful DPN can potentially reduce pain and improve quality of life.

Guidelines

Various guidelines for the treatment of DPN, neuropathic pain, PHN, and restless legs syndrome recommend gabapentin or pregabalin immediate-release as treatment options.[4-11] Guidelines do not address pregabalin extended-release tablets.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of pregabalin extended-release tablets. Additionally, due to the availability of generic pregabalin extended-release tablets, approval of a branded pregabalin extended-release product requires a previous trial of the generic. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of pregabalin extended-release tablets is recommended in those who meet one of the following criteria:

FDA-Approved Indications

62. Neuropathic Pain Associated with Diabetic Peripheral Neuropathy. Approve pregabalin extended-release tablets for 1 year if the patient meets the following criteria (A and B):

- **A)** Patient has tried gabapentin immediate-release (brand [Neurontin] or generic) or generic immediate-release pregabalin; AND
- **B)** If brand Lyrica CR is requested, the patient meets BOTH of the following (i and ii):
  - **i.** Patient has tried generic pregabalin extended-release tablets; AND
  - **ii.** Patient cannot continue to use the generic due to a formulation difference in the inactive ingredient(s) [e.g., differences in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which, according to the prescriber, would result in a significant allergy or serious adverse reaction.

63. Postherpetic Neuralgia. Approve pregabalin extended-release tablets for 1 year if the patient meets the following criteria (A and B):

- **A)** Patient has tried gabapentin immediate-release (brand [Neurontin] or generic) or generic immediate-release pregabalin; AND
- **B)** If brand Lyrica CR is requested, the patient meets BOTH of the following (i and ii):
  - **i.** Patient has tried generic pregabalin extended-release tablets; AND
  - **ii.** Patient cannot continue to use the generic due to a formulation difference in the inactive ingredient(s) [e.g., differences in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which, according to the prescriber, would result in a significant allergy or serious adverse reaction.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of pregabalin extended-release tablets is not recommended in the following situations:

114. Fibromyalgia. A double-blind, placebo-controlled, randomized withdrawal trial of pregabalin extended-release tablets in adults with fibromyalgia failed to demonstrate efficacy.[1]

115. Partial Onset Seizures. A double-blind, placebo-controlled, randomized trial of pregabalin extended-release tablets as adjunctive therapy in adults with partial onset seizures failed to demonstrate efficacy.[1]

116.

117. Restless Legs Syndrome. No data are available for pregabalin extended-release tablets for the treatment of restless legs at this time.

118. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

A) POLICY: Neurology – Oxybate Products Prior Authorization Policy
- Lumryz™ (sodium oxybate extended-release oral suspension – Avadel)
- Xyrem® (sodium oxybate oral solution – Jazz, generic)
- Xywav® (calcium, magnesium, potassium, and sodium oxybates oral solution – Jazz)

REVIEW DATE: 06/14/2023

OVERVIEW

Lumryz, sodium oxybate oral solution, and Xywav, central nervous system (CNS) depressants, are indicated for the following uses:[1-3]

- **Cataplexy treatment in patients with narcolepsy**. Sodium oxybate oral solution and Xywav are indicated in patients ≥ 7 years of age, and Lumryz is indicated in adults.
- **Excessive daytime sleepiness in narcolepsy**. Sodium oxybate oral solution and Xywav are indicated in patients ≥ 7 years of age, and Lumryz is indicated in adults.

Additionally, Xywav is indicated for the treatment of **idiopathic hypersomnia** in adults.[2]

Two specialized tests, which can be performed in a sleep disorders clinic, are required to establish a diagnosis of narcolepsy or idiopathic hypersomnia.[4] Polysomnography is an overnight recording of brain and muscle activity, breathing, and eye movements. The multiple sleep latency test (MSLT) assesses daytime sleepiness by measuring how quickly a person falls asleep and whether they enter rapid eye movement (REM) sleep. Polysomnography is routinely indicated for the diagnosis of sleep-related breathing disorders; for continuous positive airway pressure titration in patients with sleep-related breathing disorders; with an MSLT in the evaluation of suspected narcolepsy; and in certain atypical or unusual parasomnias.[5] The MSLT is indicated as part of the evaluation of patients with suspected narcolepsy to confirm the diagnosis or patients who are thought to have idiopathic hypersomnia to exclude other causes of hypersomnia. Most patients with narcolepsy have objective evidence of hypersomnia as determined by a mean sleep latency < 5 minutes. In studies, the presence of two or more sleep-onset REM episodes (SOREMPs) was associated with a sensitivity of 0.78 and a specificity of 0.93 for the diagnosis of narcolepsy. SOREMPs do not occur exclusively in patients with narcolepsy; thus, it is important to rule out or treat other sleep disorders before evaluating SOREMPs in the diagnosis of narcolepsy. Diagnostic criteria for patients with idiopathic hypersomnia include a mean sleep latency ≤ 8 minutes and MSLT results showing < 2 SOREMPs or no SOREMPs if the REM sleep latency preceding polysomnogram is ≤ 15 minutes; also, these patients do not have cataplexy. For these reasons, polysomnography and an MSLT performed on the day after the polysomnographic evaluation are routinely indicated in the evaluation of suspected narcolepsy or idiopathic hypersomnia.

Guidelines

Pertinent medical guidelines related to oxybate products are summarized below; of note, Lumryz and Xywav are not addressed in any of the guidelines.

Narcolepsy and Cataplexy

The American Academy of Sleep Medicine (AASM) practice parameters for the treatment of central disorders of hypersomnolence were updated in 2021.[6,7]

- Modafinil, Wakix® (pitolisant tablets), sodium oxybate, and Sunosi® (solriamfetol tablets) are recommended as effective treatments for daytime sleepiness due to narcolepsy and reducing disease severity in adults (Strong Recommendation for each).
- Wakix and sodium oxybate have also demonstrated efficacy for the treatment of cataplexy in patients with narcolepsy (Strong Recommendation for each).
- Sodium oxybate and armodafinil have Conditional Recommendations for the treatment of narcolepsy, showing efficacy for daytime sleepiness due to narcolepsy and reducing disease severity.
- Dextroamphetamine has a Conditional Recommendation for the treatment of narcolepsy, showing efficacy for excessive daytime sleepiness and cataplexy.
- Methylphenidate has a Conditional Recommendation for the treatment of narcolepsy, showing efficacy in reducing disease severity.
- There was insufficient and inconclusive evidence to make recommendations for l-carnitine, scheduled naps, selegiline, triazolam, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs).
- Modafinil and sodium oxybate have Conditional Recommendations for the treatment of narcolepsy in pediatric patients.

Note: A Strong Recommendation should be followed by clinicians under most circumstances. A Conditional Recommendation requires that the clinician use clinical knowledge and experience and strongly consider the individual patient's values and preferences to determine the best course of action.

Idiopathic Hypersomnia

The AASM guideline includes recommendations for the treatment of idiopathic hypersomnia.[6,7]

- Only modafinil has a Strong recommendation for use.
- Clarithromycin, methylphenidate, Wakix, and sodium oxybate have Conditional recommendations for the treatment of idiopathic hypersomnia in adults.

Safety

Sodium oxybate is the sodium salt of gamma hydroxybutyrate (GHB) and Xywav is a mixed salt formulation of GHB.[1-3] They are both Schedule III controlled substances. Abuse of GHB (a Schedule I controlled substance), either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. Because of the risks of CNS depression, abuse, and misuse, sodium oxybate oral solution and Xywav are available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the Xyrem/Xywav Success Program, using a centralized pharmacy. Healthcare professionals who prescribe sodium oxybate oral solution or Xywav and patients must enroll in the Xyrem/Xywav Success Program and must comply with the requirements to ensure the drug's safe use. Similarly, Lumryz is only available through a restricted distribution program under a REMS called the Lumryz REMS. Healthcare providers who prescribe Lumryz must be specially certified; Lumryz will be dispensed only by pharmacies that are specially certified; and Lumryz will be dispensed and shipped only to patients who are enrolled in the Lumryz REMS with documentation of safe use conditions.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lumryz, sodium oxybate oral solution, and Xywav. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lumryz, sodium oxybate oral solution, and Xywav as well as the monitoring required for adverse event and long-term efficacy, approval requires these products to be prescribed by a physician who specializes in the condition being treated.

Automation: Continuation of Therapy is not clinically necessary for the Oxybate Products. Refer to the AUM reference guide for additional information.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lumryz, sodium oxybate oral solution, or Xywav is recommended in those who meet one of the following criteria:

FDA-Approved Indications

21. Cataplexy Treatment in a Patient with Narcolepsy. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):

- **B)** Patient is ≥ 7 years of age (sodium oxybate oral solution and Xywav) or ≥ 18 years of age (Lumryz); AND
- **C)** Patient has been evaluated using polysomnography and a multiple sleep latency test; AND
- **D)** Diagnosis of narcolepsy has been confirmed, according to the prescriber; AND
- **E)** The medication has been prescribed by a sleep specialist physician or a neurologist; AND
- **F)** Patient meets ONE of the following criteria (i or ii);
  - **i.** Patient has tried dextroamphetamine; OR
  - **ii.** Patient has a contraindication or intolerance to dextroamphetamine, according to the prescriber. Note: Contraindications to dextroamphetamine include a of substance use disorder; advanced arteriosclerosis, symptomatic cardiovascular disease, and/or moderate to severe hypertension; hyperthyroidism; known hypersensitivity to sympathomimetic amines; glaucoma; agitated states; and concomitant administration with monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs.

22. Excessive Daytime Sleepiness in a Patient with Narcolepsy. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):

- **A)** Patient is ≥ 7 years of age (sodium oxybate oral solution and Xywav) or ≥ 18 years of age (Lumryz); AND
- **B)** Patient has been evaluated using polysomnography and a multiple sleep latency test; AND
- **C)** Diagnosis of narcolepsy has been confirmed, according to the prescriber; AND
- **D)** The medication has been prescribed by a sleep specialist physician or a neurologist; AND
- **E)** Patient has tried at least one of the following treatments: a central nervous system (CNS) stimulant, modafinil, or armodafinil.
  Note: Examples of CNS stimulants include methylphenidate, dexmethylphenidate, and dextroamphetamine.

23. Idiopathic Hypersomnia. Approve Xywav (NOT sodium oxybate oral solution or Lumryz) for 1 year if the patient meets the following criteria (A, B, C, D, and E):

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has been evaluated using polysomnography and a multiple sleep latency test; AND
- **C)** Results of the polysomnography and a multiple sleep latency test are congruent with a diagnosis of idiopathic hypersomnia, according to the prescriber; AND
- **D)** The medication has been prescribed by a sleep specialist physician or a neurologist; AND
- **E)** Patient has tried at least one of modafinil, armodafinil, or methylphenidate.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lumryz, sodium oxybate oral solution or Xywav is not recommended in the following situations:

119. **Fibromyalgia.** The European League Against Rheumatism (EULAR) issued evidence-based recommendations for the management of fibromyalgia (2016) stating that initial management should involve patient education and focus on non-pharmacological therapies.[7] EULAR's position on sodium oxybate for fibromyalgia is strongly against with 94% agreement. Duloxetine, pregabalin capsules and oral solution, and Savella® (milnacipran tablets) are indicated for the treatment of fibromyalgia.[9-11] Other recommended treatments include tricyclic antidepressants (i.e., amitriptyline), cyclobenzaprine, gabapentin, and selective serotonin reuptake inhibitors (i.e., fluoxetine, sertraline, paroxetine).[12]

120. **Concomitant use of Lumryz, sodium oxybate oral solution, and/or Xywav with each other or an oxybate product used in combination with Wakix (pitolisant tablets) and/or Sunosi (solriamfetol tablets).** Lumryz, sodium oxybate oral solution. and Xywav have the same active ingredient (oxybate, a CNS depressant) and have not been studied for use in combination or as alternating treatments.[1-3] Sunosi, a dopamine and norepinephrine reuptake inhibitor, is indicated to improve wakefulness in adults with excessive daytime sleepiness due to narcolepsy or obstructive sleep apnea.[13] Wakix, an antagonist/inverse agonist of the histamine-3 receptor, is indicated for excessive daytime sleepiness and cataplexy in adults with narcolepsy.[14] Currently, there are no published studies evaluating combination use of these medications.

121. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Neurology – Qalsody Prior Authorization Policy
- Qalsody™ (tofersen intrathecal injection – Biogen)

REVIEW DATE: 05/24/2023

OVERVIEW

Qalsody, an antisense oligonucleotide, is indicated for the treatment of **amyotrophic lateral sclerosis (ALS)** in adults who have a **mutation** in the **superoxide dismutase 1 (SOD1) gene**.[1]

Guidelines

The American Academy of Neurology (AAN) practice parameter on the care of patients with ALS (last updated 2009; reaffirmed 2023) does not address Qalsody, Relyvrio, Radicava ORS, or Radicava IV.[2,3] The practice parameter states that riluzole is safe and effective for slowing disease progression to a modest degree and should be offered to patients with ALS. However, riluzole may result in fatigue in some patients and if the risk of fatigue outweighs modest survival benefits, discontinuation of riluzole may be considered. Referral to a specialized multidisciplinary clinic should be considered for patients with ALS to optimize health care delivery, prolong survival, and enhance quality of life.

The European Federation of Neurological Societies (EFNS) guidelines on the clinical management of ALS (2012) also recommend patients be offered treatment with riluzole as early as possible after diagnosis.[4] Qalsody is not mentioned in these guidelines. The Canadian best practice recommendations for the management of ALS state that riluzole has demonstrated efficacy in improving survival in ALS and there is evidence that riluzole prolongs survival by a median duration of 3 months.[5] Riluzole should be started soon after the diagnosis of ALS. In a select group of patients, Radicava has been shown to slow decline on the ALS Functional Rating Scale-Revised (ALSFRS-R) scores compared against intravenous (IV) placebo over a 6-month period. The following patients have demonstrated a benefit of Radicava: patients with a disease duration < 2 years, forced vital capacity > 80%, all ALSFRS-R subcomponent scores > 2, and patients who have demonstrated steady decline in the ALSFRS-R over a 3-month period. Evidence for benefit of Radicava IV at other stages of ALS have not been demonstrated. Risks and benefits as well as individualized goals should be considered and discussed before starting therapy with Radicava IV. Qalsody is not mentioned in these guidelines.

POLICY STATEMENT

Due to the lack of clinical efficacy data, **approval is not recommended** for Qalsody.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Qalsody are not recommended in the following situations:

122. Amyotrophic Lateral Sclerosis (ALS). Approval is not recommended due to the unclear clinical benefit of Qalsody and lack of clinical efficacy data. In its pivotal trial (VALOR), no significant difference was observed between Qalsody and placebo in the primary endpoint of change in the ALSFRS-R score, which is a measure of ALS functional status.[6] The preliminary evidence demonstrated that Qalsody led to greater reduction of mean concentration of plasma neurofilament light chains (a marker of axonal injury and neurodegeneration) [secondary endpoint] compared with placebo. However, it is unknown if decreases in the surrogate biomarker of neurofilament light chain levels improve outcomes for patients. Results from the open-label extension trial and ongoing Phase III trial (ATLAS) are needed to determine whether Qalsody provides clinically meaningful benefit in patients with *SOD1-ALS* and to more clearly define an appropriate population for this therapy.

123. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Neurology – Radicava Products Prior Authorization Policy
- Radicava® (edaravone intravenous infusion – Mitsubishi Tanabe)
- Radicava ORS® (edaravone oral suspension – Mitsubishi Tanabe)

REVIEW DATE: 04/19/2023

OVERVIEW

Radicava intravenous (IV) and Radicava ORS are indicated for the treatment of **amyotrophic lateral sclerosis** (ALS).[1,14]

Edaravone is an anti-oxidative, free radical scavenger which eliminates lipid peroxide and hydroxyl radicals; however, it is unknown exactly how edaravone exerts its therapeutic effect in ALS.[1-2]

Clinical Efficacy

The efficacy of Radicava IV was evaluated in one Phase III, randomized, double-blind, placebo-controlled, Japanese trial (published) [n = 137].[2] This study enrolled patients who had a "definite" or "probable" diagnosis of ALS (based on El Escorial and revised Airlie House criteria; criteria provided in the Appendix) and were living independently at the time of screening. Patients also were required to have functionally retained most activities of daily living (defined as a score of two points or better on each individual item of the ALS Functional Rating Scale – Revised [ALSFRS-R]), have normal respiratory function (i.e., a percent-predicted forced vital capacity [FVC] value ≥ 80%), and have a disease duration of ≤ 2 years. Overall, 91% of patients were also receiving riluzole. The decline in the ALSFRS-R scores from baseline to Week 24 was statistically significantly less with Radicava IV compared with placebo.[1,2] In a separate study involving patients with longer disease duration, reduced respiratory function, and less certain ALS diagnosis, Radicava IV did not demonstrate benefit vs. placebo.[3]

Radicava ORS received FDA-approval under the 505(b)(2) approval pathway which relied upon evaluations of safety and efficacy for Radicava IV.[14]

Guidelines

The American Academy of Neurology (AAN) practice parameter on the care of patients with ALS (last updated 2009; reaffirmed 2023) does not yet address Radicava IV or Radicava ORS.[4-5] The practice parameter states that riluzole is safe and effective for slowing disease progression to a modest degree and should be offered to patients with ALS. However, riluzole may result in fatigue in some patients and if the risk of fatigue outweighs the modest survival benefits, discontinuation of riluzole may be considered. Referral to a specialized multidisciplinary clinic should be considered for patients with ALS to optimize health care delivery, prolong survival, and enhance quality of life. Additionally, noninvasive mechanical ventilation may lengthen survival and can be considered to improve quality of life and slow FVC decline. The European Federation of Neurological Societies guidelines on the clinical management of ALS (2012) also recommend patients be offered treatment with riluzole as early as possible after diagnosis.[6] However, patients with progressive muscular atrophy, primary lateral sclerosis, or hereditary spastic paraplegia should not be treated with riluzole.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Radicava IV or Radicava ORS. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Radicava IV or Radicava ORS as well as the monitoring required for adverse events and long-term efficacy, approval requires Radicava IV or Radicava ORS to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Radicava IV or Radicava ORS is recommended in those who meet the following criteria:

FDA-Approved Indication

2. **Amyotrophic Lateral Sclerosis (ALS).** Approve for 6 months if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, iv, v, and vi):
     - i. According to the prescriber, the patient has a "definite" or "probable" diagnosis of amyotrophic lateral sclerosis (ALS) based on the application of the El Escorial or the revised Airlie House diagnostic criteria; AND
     - ii. Patient has a score of two points or more on each item of the ALS Functional Rating Scale – Revised (ALSFRS-R) [i.e., has retained most or all activities of daily living]; AND
     - iii. Patient has a percent-predicted forced vital capacity (FVC) ≥ 80% (i.e., has normal respiratory function); AND
     - iv. Patient has been diagnosed with ALS for ≤ 2 years; AND
     - v. Patient has received or is currently receiving riluzole tablets, Tiglutik (riluzole oral suspension), or Exservan (riluzole oral film); AND
     - vi. The medication is prescribed by or in consultation with a neurologist, a neuromuscular disease specialist, or a physician specializing in the treatment of ALS.
   - **B)** Patient is Currently Receiving Radicava IV or Radicava ORS. Approve if the patient meets ALL of the following (i, ii, and iii):
     - i. Patient does not require invasive ventilation; AND
     - ii. According to the prescriber, the patient continues to benefit from therapy; AND
     - iii. The medication is prescribed by or in consultation with a neurologist, a neuromuscular disease specialist, or a physician specializing in the treatment of ALS.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Radicava IV and Radicava ORS are not recommended in the following situations:

124. **Aneurysmal Subarachnoid Hemorrhage.** Radicava IV and Radicava ORS are not indicated for the treatment of aneurysmal subarachnoid hemorrhage (SAH).[1,14] One randomized controlled study (published) [n = 91] evaluated the efficacy of Radicava (formulation/dose not specified) in patients with aneurysmal SAH.[7] At 3 months post-SAH, the incidence of delayed ischemic neurologic deficits (DINDs) in patients treated with Radicava was 10% vs. 21% in patients in a control group; the between-group treatment difference was not significant. In patients who had DINDs, 66% of patients in the control group had a cerebral infarction caused by vasospasm compared with 0% of Radicava-treated

patients (P = 0.028). Additional, well-designed clinical studies are needed to establish if Radicava has a role in therapy post-SAH.

65.

125. Myocardial Infarction. Radicava IV and Radicava ORS are not indicated for the treatment of myocardial infarction; there are no US or North American studies of Radicava IV or Radicava ORS for this indication.[1,14] One randomized, placebo-controlled, open-label, Japanese study (published) [n = 101] evaluated the effect of Radicava IV on the long term prognosis in patients experiencing an acute myocardial infarction.[8] Patients were randomized to receive either Radicava IV (foreign formulation) 30 mg or placebo immediately prior to reperfusion. In all patients, successful reperfusion was obtained within 6 hours post-symptom onset. Radicava IV significantly attenuated the infarct size and incidence of reperfusion arrhythmia compared with placebo (P = 0.035 and P = 0.031, respectively).

126. Radiation-Induced Brain Injury. Radicava IV and Radicava ORS are not indicated for the treatment of radiation-induced brain injury; there are no US or North American studies of Radicava IV or Radicava ORS for this indication.[1,14] One randomized, open-label, 3-month, Chinese study (published) [n = 137] evaluated the protective effect of Radicava IV on radiation-induced brain necrosis in patients with nasopharyngeal carcinoma.[9] Patients were randomized to receive Radicava IV (foreign formulation) 30 mg twice daily for 2 weeks (not FDA-approved dosing) + IV corticosteroid therapy or placebo + IV corticosteroid therapy. Following 3 months of therapy, radiologic improvement (reduction in edema of ≥ 25%) was observed in 55.6% of patients who received Radicava IV (n = 40/72) compared with 35.4% of patients treated with placebo (n = 23/65) [P = 0.025]. The area of T1-weighted contrast enhancement was reduced from baseline with both Radicava IV and placebo (-1.67 cm and -1.20 cm, respectively); however, the difference between the treatment arms was not statistically significant. Improvement in neurologic signs and symptoms evaluated by the Late Effects of Normal Tissues – Subjective, Objective, Management, Analytic (LENT/SOMA) scale was also observed in 61.1% of Radicava IV-treated patients vs. 38.5% of placebo-treated patients (P = 0.006). Further research is warranted to determine if Radicava IV has a place in therapy in the treatment of radiation-induced brain injury.

127. Retinal Vein Occlusion. Radicava IV and Radicava ORS are not indicated for the prevention of macular edema and improvement of visual acuity after arteriovenous sheathotomy in patients with branch retinal vein occlusion; there are no US or North American studies of Radicava IV or Radicava ORS for this indication.[1,14] A single, small, prospective, Japanese study [published] (n = 47) evaluated the efficacy of Radicava IV (foreign formulation) in patients with branch retinal vein occlusion undergoing vitrectomy.[10] Patients either received Radicava IV 30 mg at the time of the procedure or no additional therapy. Visual acuity was measured before and 12 months after the procedure. At 12 months following the operation, the logarithm of the minimum angle of resolution (logMAR) units improved from 0.22 to 0.56 logMAR units in patients who had received Radicava IV and from 0.20 to 0.27 logMAR units in patients who did not receive active treatment (P = 0.016). Additional data are needed to support the use of Radicava IV for this indication.

128. Sensorineural Hearing Loss. Radicava IV and Radicava ORS are not indicated for the treatment of sensorineural hearing loss; there are no US-based studies of Radicava IV or Radicava ORS for this indication.[1,14] One small, Japanese study evaluated 14 patients with idiopathic sudden sensorineural hearing loss treated with Radicava IV (foreign formulation; dose not specified).[11] These patients were compared with a control group of 14 patients with similar prognostic factors who had been treated with hyperbaric oxygenation therapy. No significant differences were observed between the Radicava IV group and the control group.

129. Stroke. Radicava IV and Radicava ORS are not FDA-approved for the treatment of patients who have experienced stroke.[1,14] Radicava IV has been approved in other countries for this indication and there are some foreign data supporting its use.[12] There are no US-based studies of Radicava IV for stroke at this time. A systematic review assessed available efficacy data from three clinical trials (n = 496) of Radicava IV for acute ischemic stroke.[13] These trials compared Radicava IV 30 mg twice daily for 14 days + another treatment vs. the other treatment alone within 72 hours of stroke symptom onset. One trial did not find significantly reduced mortality with Radicava IV vs. the control group; the other two studies did not report this endpoint. Overall, there was a significantly higher proportion of patients who had neurologic improvement in the Radicava IV group vs. control.

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130. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX*

El Escorial criteria for the diagnosis of ALS were initially developed by the World Federation of Neurology (WFN) in 1990. In 1998, the WFN held a workshop for the Research Committee on Motor Neuron Diseases at the Airlie Conference Center in Virginia, which resulted in a revision of the guidelines in 2000. The pivotal study of Radicava IV references the El Escorial criteria updated by the WFN in 2000 (Airlie House). According to these guidelines, the diagnosis of ALS requires:

The presence of:

- Evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiological or neuropathologic examination; AND
- Evidence of upper motor neuron (UMN) degeneration by clinical examination; AND
- Progressive spread of symptoms or signs within a region or to other regions, as determined by or examination.

Together with the absence of:

1. Electrophysiological or pathological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration; AND
2. Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.

Without pathological confirmation, the diagnosis of ALS may be categorized into levels of certainty using clinical assessment. The following terms are used to describe the categories of diagnostic certainty.

- **Clinically Definite ALS:** defined on clinical evidence alone by the presence of UMN, as well as LMN signs, in the bulbar region and at least two spinal regions or the presence of UMN and LMN signs in three spinal regions.
- **Clinically Probable ALS:** defined on clinical evidence alone by UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs.
- **Clinically Probable ALS – Laboratory-supported:** defined when clinical signs of UMN and LMN dysfunction are in only one region, or when UMN signs alone are present in one region, and LMN signs defined by EMG criteria are present in at least two regions, with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.
- **Clinically Possible ALS:** defined when clinical signs of UMN and LMN dysfunction are found together in only one region or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs and the diagnosis of Clinically Probable ALS – Laboratory supported cannot be proven by evidence on clinical grounds in conjunction with electrodiagnostic, neurophysiologic, neuroimaging or clinical laboratory studies. Other diagnoses must have been excluded to accept a diagnosis of Clinically Possible ALS.

*** This appendix is for reference; it is NOT intended that patients meet the above criteria for approval of Radicava IV or Radicava ORS.**

PRIOR AUTHORIZATION POLICY

POLICY: Neurology – Relyvrio Prior Authorization Policy
- Relyvrio™ (sodium phenylbutyrate and taurursodiol powder for oral suspension – Amylyx)

REVIEW DATE: 11/15/2023

OVERVIEW
Relyvrio, a combination product of sodium phenylbutyrate and taurursodiol, is indicated for the treatment of **amyotrophic lateral sclerosis** (ALS) in adults.[1]

Guidelines
The American Academy of Neurology practice parameter on the care of patients with ALS (last updated 2009; reaffirmed 2023) does not yet address Relyvrio; Radicava is also not addressed.[2,3] The practice parameter states that riluzole is safe and effective for slowing disease progression to a modest degree and should be offered to patients with ALS. However, riluzole may result in fatigue in some patients and if the risk of fatigue outweighs modest survival benefits, discontinuation of riluzole may be considered. Referral to a specialized multidisciplinary clinic should be considered for patients with ALS to optimize health care delivery, prolong survival, and enhance quality of life. Additionally, noninvasive mechanical ventilation may lengthen survival and can be considered to improve quality of life and slow forced vital capacity decline. The European Federation of Neurological Societies guidelines on the clinical management of ALS (2012) also recommend patients be offered treatment with riluzole as early as possible after diagnosis.[4] However, patients with progressive muscular atrophy, primary lateral sclerosis, or hereditary spastic paraplegia should not be treated with riluzole. New guidelines on the management of ALS were presented at the European Academy of Neurology 2023 meeting and are expected to be published before the end of 2023.[5] The recommendations during this meeting stated the riluzole should be offered lifelong to all ALS patients at diagnosis and a single daily dose of 50 mg can be effective.[7] The Canadian best practice recommendations for the management of ALS state that riluzole has demonstrated efficacy in improving survival in ALS and there is evidence that riluzole prolongs survival by a median duration of 3 months.[6] Riluzole should be started soon after the diagnosis of ALS.

POLICY STATEMENT
Due to the lack of clinical efficacy data, **approval is not recommended** for Relyvrio.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Relyvrio is not recommended in the following situations:

131. Amyotrophic Lateral Sclerosis (ALS). Approval is not recommended due to the unclear clinical benefit of Relyvrio and lack of clinical efficacy data.[7] The preliminary evidence demonstrates a

potentially minimal clinical benefit that is confounded to interpret (e.g., two-point difference in the ALS functional rating scale – revised [ALSFRS-R] mean score). The efficacy data for Relyvrio are not convincing and have many limitations in analysis. Results from the ongoing Phase III trial (PHOENIX) are needed to determine whether Relyvrio provides clinically meaningful benefit in patients with ALS and to more clearly define an appropriate population for this therapy.

132. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Neurology – Riluzole Products Prior Authorization Policy
- Exservan™ (riluzole oral film – Mitsubishi Tanabe Pharma America)
- Rilutek® (riluzole tablets – Covis Pharma, generic)
- Tiglutik® (riluzole oral suspension – ITF Pharma)

REVIEW DATE: 08/30/2023

OVERVIEW

All of the available riluzole products are indicated for the treatment of **amyotrophic lateral sclerosis** (ALS).[1-3]

Guidelines

The American Academy of Neurology (AAN) practice parameter on the care of patients with ALS (last updated 2009; reaffirmed 2023) states that riluzole should be offered to patients with ALS (Level A recommendation), as it is safe and effective for modestly slowing disease progression.[4,5] Based on available clinical trial data, the AAN estimates riluzole prolongs survival by 2 to 3 months. However, some large cohort studies estimate survival to be prolonged for up to 21 months. The European Federation of Neurological Societies guidelines on the clinical management of ALS (2012) also recommend patients be offered treatment with riluzole as early as possible after diagnosis.[6] While it is noted that riluzole may be less effective in patients with late-stage disease, it is unclear when or if treatment should be discontinued. New guidelines on the management of ALS were presented at the European Academy of Neurology 2023 meeting and are expected to be published before the end of 2023.[7] The recommendations during this meeting stated the riluzole should be offered lifelong to all ALS patients at diagnosis and a single daily dose of 50 mg can be effective.[7] The Canadian best practice recommendations for the management of ALS state that riluzole has demonstrated efficacy in improving survival in ALS and there is evidence that riluzole prolongs survival by a median duration of 3 months.[8] Riluzole should be started soon after the diagnosis of ALS.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of riluzole. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with riluzole as well as the monitoring required for adverse events and long-term efficacy, approval requires riluzole to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of riluzole is recommended in those who meet the following criteria:

FDA-Approved Indication

165. Amyotrophic Lateral Sclerosis (ALS). Approve for 1 year if the agent is prescribed by or in consultation with a neurologist, a neuromuscular disease specialist, or a physician specializing in the treatment of ALS.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of riluzole is not recommended in the following situations:

256. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Neurology – Rystiggo Prior Authorization Policy
- Rystiggo® (rozanolixizumab-noli subcutaneous infusion – UCB)

REVIEW DATE: 07/05/2023; selected revision 10/18/2023

OVERVIEW

Rystiggo, a neonatal Fc receptor blocker, is indicated for the treatment of **generalized myasthenia gravis** in adults who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody-positive.[1]

Disease Overview

Myasthenia gravis is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body, including the arms and legs.[2] Myasthenia gravis is caused by the production of pathogenic immunoglobulin G (IgG) autoantibodies against neuromuscular junction components (AChR, MuSK, and low density lipoprotein receptor-related protein 4 [LRP4]).[3] Approximately 85% of patients with myasthenia gravis are anti-AChR antibody-positive and approximately 5% to 8% of patients are anti-MuSK antibody-positive.[4] The result of the antibodies at the junction is unsuccessful nerve transmission and deficiency or weakness of muscle contractions.[3] The hallmark of myasthenia gravis is muscle weakness that worsens after periods of activity and improves after periods of rest.[2] Certain muscles such as those that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are often involved in the disorder; however, the muscles that control breathing and neck and limb movements may also be affected.

Clinical Efficacy

The efficacy of Rystiggo was evaluated in an 18-week, multicenter, randomized, double-blind, placebo-controlled trial in adults with anti-AChR or anti-MuSK antibody-positive generalized myasthenia gravis (n = 200).[1,5] Two doses of Rystiggo were studied: 7 mg/kg and 10 mg/kg. Among other criteria, patients in the study had a Myasthenia Gravis Foundation of America classification of II to IVa and a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 3, with at least 3 points from non-ocular symptoms. MG-ADL assesses the impact of generalized myasthenia gravis on daily functions of eight signs or symptoms that are typically impacted by this disease. Each sign or symptom is assessed on a 4-point scale; a higher score indicates greater impairment. At baseline, over 83% of patients received acetylcholinesterase inhibitors, over 50% of patients received oral steroids, and approximately 50% received non-steroidal immunosuppressant therapies, at stable doses. The primary endpoint was the change from baseline to Day 43 in the MG-ADL total score. Statistically significantly greater improvement in the MD-ADL score was observed in both Rystiggo 7 mg/kg and Rystiggo 10 mg/kg groups vs. placebo: -3.4 points in the Rystiggo-treated group at either dose vs. -0.8 points in the placebo group ($P < 0.001$). Statistically significant improvement in the secondary efficacy endpoints were also observed in the Rystiggo groups vs. placebo.

Guidelines

An international consensus guidance for the management of myasthenia gravis was published in 2016.[6] The guidelines recommend pyridostigmine for the initial treatment in most patients with myasthenia gravis. The ability to discontinue pyridostigmine can indicate that the patient has met treatment goals and may guide the tapering of other therapies. Corticosteroids or immunosuppressant therapy should be used in all patients with myasthenia gravis who have not met treatment goals after an adequate trial of pyridostigmine. Nonsteroidal immunosuppressant agents include azathioprine, cyclosporine, mycophenolate mofetil,

methotrexate, and tacrolimus. It is usually necessary to maintain some immunosuppression for many years, sometimes for life. Plasma exchange and intravenous immunoglobulin can be used as short-term treatments in certain patients. A 2020 update to these guidelines provides new recommendations for methotrexate, rituximab, and Soliris® (eculizumab intravenous infusion).[7] All recommendations should be considered extensions or additions to recommendations made in the initial international consensus guidance (2016). Oral methotrexate may be considered as a steroid-sparing agent in patients with generalized myasthenia gravis who have not tolerated or responded to steroid-sparing agents. Rituximab should be considered as an early therapeutic option in patients with anti-MuSK antibody-positive myasthenia gravis who have an unsatisfactory response to initial immunotherapy. Soliris should be considered in the treatment of severe, refractory, anti-AChR antibody-positive generalized myasthenia gravis.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Rystiggo. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Rystiggo as well as the monitoring required for adverse events and long-term efficacy, approval requires Rystiggo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rystiggo is recommended in those who meet the following criteria:

FDA-Approved Indication

64. Generalized Myasthenia Gravis. Approve if the patient meets ONE of the following (A or B):

H) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, iv, v, vi, and vii):

xxii. Patient is ≥ 18 years of age; AND

xxiii. Patient meets one of the following (a or b):

a) Patient has confirmed anti-acetylcholine receptor antibody-positive generalized myasthenia gravis; OR

b) Patient has confirmed anti-muscle-specific tyrosine kinase antibody-positive generalized myasthenia gravis; AND

xxiv. Patient meets both of the following (a and b):

a) Myasthenia Gravis Foundation of America class II to IV; AND

b) Myasthenia Gravis Activities of Daily Living (MG-ADL) total score ≥ 3 for non-ocular symptoms; AND

xxv. Patient meets one of the following (a or b):

a) Patient received or is currently receiving pyridostigmine; OR

b) Patient has had inadequate efficacy, a contraindication, or significant intolerance to pyridostigmine; AND

xxvi. Patient has evidence of unresolved symptoms of generalized myasthenia gravis; AND

Note: Examples of unresolved symptoms include difficulty swallowing, difficulty breathing, or a functional disability resulting in the discontinuation of physical activity (e.g., double vision, talking, impairment of mobility).

xxvii. Treatment cycles are no more frequent than every 63 days from the start of the previous treatment cycle; AND

xxviii. The medication is being prescribed by or in consultation with a neurologist.

I) Patient is Currently Receiving Rystiggo. Approve for 1 year if the patient meets the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Patient is continuing to derive benefit from Rystiggo, according to the prescriber; AND
Note: Examples of derived benefit include reductions in exacerbations of myasthenia gravis; improvements in speech, swallowing, mobility, and respiratory function.

iii. Treatment cycles are no more frequent than every 63 days from the start of the previous treatment cycle; AND

iv. The medication is being prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rystiggo is not recommended in the following situations:

257. Concomitant Use with Another Neonatal Fc Receptor Blocker, a Complement Inhibitor, or a Rituximab Product. There is no evidence to support concomitant use of Rystiggo with another neonatal Fc receptor blocker, a complement inhibitor, or a rituximab product.

ZZZ) Note: Examples of neonatal Fc receptor blockers are Vyvgart (efgartigimod alfa-fcab intravenous infusion] and Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection).

AAAA) Note: Examples of complement inhibitors are Soliris (eculizumab intravenous infusion), Ultomiris (ravulizumab-cwvz intravenous infusion or subcutaneous injection), and Zilbrysq (zilucoplan subcutaneous injection).

BBBB)

258. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Neurology – Skyclarys Prior Authorization Policy
- Skyclarys® (omaveloxolone capsules – Reata)

REVIEW DATE: 04/19/2023; selected revision 05/24/2023

OVERVIEW

Skyclarys, a nuclear factor (erythroid-derived 2)-like 2 (Nrf2) activator, is indicated for the treatment of Friedreich's ataxia in patients ≥ 16 years of age.[1]

Disease Overview

Friedreich's ataxia is an autosomal recessive, progressive, neurodegenerative disorder.[2-6] In the setting of clinical suspicion due to symptoms (e.g., ataxia, cardiomyopathy, scoliosis, and/or diabetes), genetic testing is the cornerstone of confirming a diagnosis of Friedreich's ataxia. A trinucleotide repeat expansion assay to detect biallelic mutations is used.

Clinical Efficacy

In the pivotal study of Skyclarys, patients were 16 to 40 years of age with genetically confirmed Friedreich's ataxia.[1,7] They were required to have a baseline modified Friedreich's Ataxia Rating Scale (mFARS) between 20 and 80. Patients with pes cavus were allowed to enroll in the study, but their participation was limited to 20% of patients and the primary efficacy analysis did not include patients with pes cavus. Patients with a B-type natriuretic peptide (BNP) > 200 pg/mL or a left ventricular ejection fraction < 40% were also excluded from the study. Uncontrolled diabetes mellitus, defined in a non-pivotal study as a hemoglobin A1c (HbA_{1c}) > 11%, was also part of the exclusion criteria for the pivotal trial.[7,8] The vast majority of patients enrolled in the pivotal trial were ambulatory (93%). The primary efficacy was measured using the mFARS.

Guidelines

Available consensus guidelines on Friedreich's ataxia (2022) identify Skyclarys as a potential investigative agent, but do not make any specific recommendations regarding its use.[6] According to guidelines, patients with Friedreich's ataxia should have an electrocardiogram (EKG) and an echocardiogram at diagnosis and then at least annually. Patients should also be evaluated annually for diabetes mellitus. There is no cure for Friedreich's ataxia; guidelines make extensive recommendations regarding management of the symptoms and complications related to the disease, including diabetes mellitus and cardiomyopathy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Skyclarys. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Skyclarys as well as the monitoring required for adverse events and long-term efficacy, approval requires Skyclarys to be prescribed by or in consultation with a physician who specializes in the condition being treated. All reviews will be forwarded to the Medical Director for evaluation.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information. Subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *Neurology – Skyclarys Prior Authorization Policy* through the Coverage Review Department, and who is requesting reauthorization, the criteria utilized do NOT require re-submission of documentation for reauthorization, except for the criterion requiring documentation of the trinucleotide repeat expansion assay genetic test confirming the diagnosis of Friedreich's ataxia.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Skyclarys is recommended in those who meet the following criteria:

FDA-Approved Indications

166. Friedreich's Ataxia. Approve for 1 year if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve if the patient meets ALL of the following criteria (i, ii, iii, iv, v, vi, and vii):
- **i.** Patient is ≥ 16 years of age; AND
- **ii.** Patient has had genetic testing confirming biallelic pathogenic variants in the frataxin (FXN) gene consistent with a diagnosis of Friedreich's ataxia **[documentation required]**; AND
- **iii.** Patient has had ALL of the following in the last year (a, b, and c):
  - **a)** Patient has a B-type natriuretic peptide (BNP) ≤ 200 pg/mL **[documentation required]**; AND
  - **b)** Patient has a left ventricular ejection fraction ≥ 40% **[documentation required]**; AND
  - **c)** Patient has a hemoglobin A_{1c} (HbA_{1c}) ≤ 11% **[documentation required]**; AND
- **iv.** Patient has been assessed using the modified Friedreich's Ataxia Rating Scale and has a score ≥ 20, but ≤ 80 **[documentation required]**; AND
- **v.** Patient is ambulatory; AND
- **vi.** Patient does not have pes cavus; AND
- **vii.** The medication is prescribed by or in consultation with a neurologist or a physician who specializes in ataxias and/or neuromuscular disorders.

B) Patient is Currently Receiving Skyclarys. Approve if the patient meets ALL of the following criteria (i, ii, iii, iv and v):
- **i.** Patient is ≥ 16 years of age; AND
- **ii.** Patient has had genetic testing confirming biallelic pathogenic variants in the frataxin (FXN) gene consistent with a diagnosis of Friedreich's ataxia **[documentation required]**; AND
- **iii.** Patient is ambulatory; AND
- **iv.** According to the prescriber, the patient continues to benefit from therapy, as demonstrated by a slowed progression on the modified Friedreich's Ataxia Rating Scale; AND
- **v.** The medication is prescribed by or in consultation with a neurologist, or a physician who specializes in ataxias and/or neuromuscular disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Skyclarys is not recommended in the following situations:

259. Metastatic Melanoma. Skyclarys has also been evaluated for the treatment of metastatic melanoma (in combination with Opdivo® [nivolumab intravenous infusion] or Yervoy® [ipilimumab intravenous infusion]).[9] Results have not been published. More data are needed.

260. Mitochondrial Myopathy. Skyclarys has also been evaluated for the treatment of mitochondrial myopathies. In one Phase II study, following 12 weeks of therapy, no differences in peak workload or 6 minute walk test were observed with Skyclarys vs. placebo.[10] More data are needed to evaluate the efficacy and safety Skyclarys for mitochondrial myopathy.

261. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Neurology – Vyvgart Hytrulo Prior Authorization Policy
- Vyvgart® Hytrulo (efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection – Argenx/Halozyme)

REVIEW DATE: 07/05/2023; selected revision 10/18/2023

OVERVIEW

Vygart Hytrulo, a neonatal Fc receptor blocker, is indicated for the treatment of **generalized myasthenia gravis** in adults who are anti-acetylcholine receptor antibody positive.[1]

Disease Overview

Myasthenia gravis is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body, including the arms and legs.[2] The hallmark of myasthenia gravis is muscle weakness that worsens after periods of activity and improves after periods of rest. Certain muscles such as those that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are often involved in the disorder; however, the muscles that control breathing and neck and limb movements may also be affected. Acquired myasthenia gravis results from the binding of autoantibodies to components of the neuromuscular junction, most commonly the acetylcholine receptor.[3]

Clinical Efficacy

Non-inferiority of Vyvgart Hytrulo to Vyvgart Intravenous was demonstrated in the ADAPT-SC study, where patients were randomized to either Vyvgart Hytrulo or Vyvgart Intravenous (n = 110).[4]

The efficacy of Vyvgart Intravenous was evaluated in a 26-week, multicenter, randomized, double-blind, placebo-controlled trial in adults with myasthenia gravis (n = 167).[5] Among other criteria, patients were on stable doses of myasthenia gravis therapy prior to screening (e.g., acetylcholinesterase inhibitors, steroids, or non-steroidal immunosuppressive therapies), either in combination or alone. In addition, patients had a Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV and a Myasthenia Gravis Activities of Daily Living (MG-ADL) total score of ≥ 5. MG-ADL assesses the impact of generalized myasthenia gravis on daily functions of eight signs or symptoms that are typically impacted by this disease. Each sign or symptom is assessed on a 4-point scale; a higher score indicates greater impairment. Patients were randomized to receive Vyvgart Intravenous or placebo. At baseline, most patients had stable doses of acetylcholinesterase inhibitors (> 80%), steroids (> 70%), and/or non-steroidal immunosuppressive therapies (about 60%). The primary efficacy endpoint was comparison of the percentage of MG-ADL responders during the first treatment cycle between treatment groups in the anti-acetylcholine receptor antibody-positive population. An MG-ADL responder was defined as a patient with a 2-point or greater reduction in the total MG-ADL score compared to the treatment cycle baseline for at least 4 consecutive weeks, with the first reduction occurring no later than 1 week after the last infusion of the cycle. Overall, 67.7% of patients who received Vyvgart Intravenous compared with 29.7% of patients who received placebo were considered MG-ADL responders (P < 0.0001).

Guidelines

An international consensus guidance for the management of myasthenia gravis was published in 2016.[3] The guidelines recommend pyridostigmine for the initial treatment in most patients with myasthenia gravis. The ability to discontinue pyridostigmine can indicate that the patient has met treatment goals and may guide the tapering of other therapies. Corticosteroids or immunosuppressant therapy should be used in all patients with myasthenia gravis who have not met treatment goals after an adequate trial of pyridostigmine. Nonsteroidal immunosuppressant agents include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. It is usually necessary to maintain some immunosuppression for many years, sometimes for life. Plasma exchange and intravenous immunoglobulin can be used as short-term treatments in certain patients. A 2020 update to these guidelines provides new recommendations for methotrexate, rituximab, and Soliris® (eculizumab intravenous infusion).[6] All recommendations should be considered extensions or additions to recommendations made in the initial international consensus guidance. Oral methotrexate may be considered as a steroid-sparing agent in patients with generalized myasthenia gravis who have not tolerated or responded to steroid-sparing agents. Rituximab should be considered as an early therapeutic option in patients with anti-muscle-specific tyrosine kinase antibody-positive myasthenia gravis who have an unsatisfactory response to initial immunotherapy. Soliris should be considered in the treatment of severe, refractory, anti-acetylcholine receptor antibody-positive generalized myasthenia gravis.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vygart Hytrulo. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vygart Hytrulo as well as the monitoring required for adverse events and long-term efficacy, approval requires Vygart Hytrulo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vyvgart Hytrulo is recommended in those who meet the following criteria:

FDA-Approved Indication

65. Generalized Myasthenia Gravis. Approve if the patient meets ONE of the following (A or B):

- **J)** Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, iv, v, vi, and vii):
  - **xxix.** Patient is ≥ 18 years of age; AND
  - **xxx.** Patient has confirmed anti-acetylcholine receptor antibody positive generalized myasthenia gravis; AND
  - **xxxi.** Patient meets both of the following (a and b):
    - **a)** Myasthenia Gravis Foundation of America classification of II to IV; AND
    - **b)** Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 5; AND
  - **xxxii.** Patient meets one of the following (a or b):
    - **a)** Patient received or is currently receiving pyridostigmine; OR
    - **b)** Patient has had inadequate efficacy, a contraindication, or significant intolerance to pyridostigmine; AND
  - **xxxiii.** Patient has evidence of unresolved symptoms of generalized myasthenia gravis; AND

Note: Examples of unresolved symptoms include difficulty swallowing, difficulty breathing, or a functional disability resulting in the discontinuation of physical activity (e.g., double vision, talking, impairment of mobility).

vi. Treatment cycles are no more frequent than every 50 days from the start of the previous treatment cycle; AND

vii. The medication is being prescribed by or in consultation with a neurologist.

K) Patient is Currently Receiving Vyvgart Hytrulo (or Vyvgart Intravenous [efgartigimod alfa-fcab intravenous infusion]). Approve for 1 year if the patient meets the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Patient is continuing to derive benefit from Vyvgart Hytrulo (or Vyvgart Intravenous), according to the prescriber; AND

Note: Examples of derived benefit include reductions in exacerbations of myasthenia gravis; improvements in speech, swallowing, mobility, and respiratory function.

iii. Treatment cycles are no more frequent than every 50 days from the start of the previous treatment cycle; AND

iv. The medication is being prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vyvgart Hytrulo is not recommended in the following situations:

262. Concomitant Use with Another Neonatal Fc Receptor Blocker, a Complement Inhibitor, or a Rituximab Product. There is no evidence to support concomitant use of Vyvgart Hytrulo with another neonatal Fc receptor blocker, a complement inhibitor, or a rituximab product.

66. Note: Examples of neonatal Fc receptor blockers are Rystiggo (rozanolixizumab-noli subcutaneous infusion) and Vyvgart (efgartigimod alfa-fcab intravenous infusion).

67. Note: Examples of complement inhibitors are Soliris (eculizumab intravenous infusion), Ultomiris (ravulizumab-cwvz intravenous infusion or subcutaneous injection), and Zilbrysq (zilucoplan subcutaneous injection).

68.

263. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Neurology – Vyvgart Intravenous Prior Authorization Policy
- Vyvgart® (efgartigimod alfa-fcab intravenous infusion – Argenx)

REVIEW DATE: 07/05/2023; selected revision 10/18/2023

OVERVIEW

Vyvgart Intravenous, a neonatal Fc receptor blocker, is indicated for the treatment of **generalized myasthenia gravis** in adults who are anti-acetylcholine receptor antibody positive.[1]

Disease Overview

Myasthenia gravis is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body, including the arms and legs.[2] The hallmark of myasthenia gravis is muscle weakness that worsens after periods of activity and improves after periods of rest. Certain muscles such as those that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are often involved in the disorder; however, the muscles that control breathing, and neck and limb movements may also be affected. Acquired myasthenia gravis results from the binding of autoantibodies to components of the neuromuscular junction, most commonly the acetylcholine receptor.[3]

Clinical Efficacy

The efficacy of Vyvgart Intravenous was evaluated in a 26-week, multicenter, randomized, double-blind, placebo-controlled trial in adults with myasthenia gravis (n = 167).[5] Among other criteria, patients were on stable doses of myasthenia gravis therapy prior to screening (e.g., acetylcholinesterase inhibitors, steroids, or non-steroidal immunosuppressive therapies), either in combination or alone. In addition, patients had a Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV and a Myasthenia Gravis Activities of Daily Living (MG-ADL) total score of ≥ 5. MG-ADL assesses the impact of generalized myasthenia gravis on daily functions of eight signs or symptoms that are typically impacted by this disease. Each sign or symptom is assessed on a 4-point scale; a higher score indicates greater impairment. Patients were randomized to receive Vyvgart Intravenous or placebo. At baseline, most patients had stable doses of acetylcholinesterase inhibitors (> 80%), steroids (> 70%), and/or non-steroidal immunosuppressive therapies (about 60%). The primary efficacy endpoint was comparison of the percentage of MG-ADL responders during the first treatment cycle between treatment groups in the anti-acetylcholine receptor antibody-positive population. An MG-ADL responder was defined as a patient with a 2-point or greater reduction in the total MG-ADL score compared to the treatment cycle baseline for at least 4 consecutive weeks, with the first reduction occurring no later than 1 week after the last infusion of the cycle. Overall, 67.7% of patients who received Vyvgart Intravenous compared with 29.7% of patients who received placebo were considered MG-ADL responders ($P < 0.0001$).

Non-inferiority of Vyvgart® Hytrulo (efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection) to Vyvgart Intravenous was demonstrated in the ADAPT-SC study, where patients were randomized to either Vyvgart Hytrulo or Vyvgart Intravenous (n = 110).[4]

Guidelines

An international consensus guidance for the management of myasthenia gravis was published in 2016.[3] The guidelines recommend pyridostigmine for the initial treatment in most patients with myasthenia gravis. The ability to discontinue pyridostigmine can indicate that the patient has met treatment goals and may guide the tapering of other therapies. Corticosteroids or immunosuppressant therapy should be used in all patients with myasthenia gravis who have not met treatment goals after an adequate trial of pyridostigmine. Nonsteroidal immunosuppressant agents include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. It is usually necessary to maintain some immunosuppression for many years, sometimes for life. Plasma exchange and intravenous immunoglobulin can be used as short-term treatments in certain patients. A 2020 update to these guidelines provides new recommendations for methotrexate, rituximab, and Soliris® (eculizumab intravenous infusion).[5] All recommendations should be considered extensions or additions to recommendations made in the initial international consensus guidance. Oral methotrexate may be considered as a steroid-sparing agent in patients with generalized myasthenia gravis who have not tolerated or responded to steroid-sparing agents. Rituximab should be considered as an early therapeutic option in patients with anti-muscle-specific tyrosine kinase antibody-positive myasthenia gravis who have an unsatisfactory response to initial immunotherapy. Soliris should be considered in the treatment of severe, refractory, anti-acetylcholine receptor antibody positive generalized myasthenia gravis.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vyvgart Intravenous. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vyvgart Intravenous as well as the monitoring required for adverse events and long-term efficacy, approval requires Vyvgart Intravenous to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vyvgart Intravenous is recommended in those who meet the following criteria:

FDA-Approved Indication

66. Generalized Myasthenia Gravis. Approve if the patient meets ONE of the following (A or B):

L) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, iv, v, vi, and vii):

xxxiv. Patient is ≥ 18 years of age; AND

xxxv. Patient has confirmed anti-acetylcholine receptor antibody-positive generalized myasthenia gravis; AND

xxxvi. Patient meets both of the following (a and b):

a) Myasthenia Gravis Foundation of America classification of II to IV; AND

b) Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 5; AND

xxxvii. Patient meets one of the following (a or b):

a) Patient received or is currently receiving pyridostigmine; OR

b) Patient has had inadequate efficacy, a contraindication, or significant intolerance to pyridostigmine; AND

xxxviii. Patient has evidence of unresolved symptoms of generalized myasthenia gravis; AND

Note: Examples of unresolved symptoms include difficulty swallowing, difficulty breathing, or a functional disability resulting in the discontinuation of physical activity (e.g., double vision, talking, impairment of mobility).

xxxix. Treatment cycles are no more frequent than every 50 days from the start of the previous treatment cycle; AND

xl. The medication is being prescribed by or in consultation with a neurologist.

M) Patient is Currently Receiving Vyvgart Intravenous (or Vyvgart Hytrulo [efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection]). Approve for 1 year if the patient meets the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Patient is continuing to derive benefit from Vyvgart Intravenous (or Vyvgart Hytrulo), according to the prescriber; AND
Note: Examples of derived benefit include reductions in exacerbations of myasthenia gravis; improvements in speech, swallowing, mobility, and respiratory function.

iii. Treatment cycles are no more frequent than every 50 days from the start of the previous treatment cycle; AND

iv. The medication is being prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vyvgart Intravenous is not recommended in the following situations:

264. Concomitant Use with Another Neonatal Fc Receptor Blocker, a Complement Inhibitor, or a Rituximab Product. There is no evidence to support concomitant use of Vyvgart Intravenous with another neonatal Fc receptor blocker, a complement inhibitor, or a rituximab product.

69. Note: Examples of neonatal Fc receptor blockers are Rystiggo (rozanolixizumab-noli subcutaneous infusion) and Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection).

70. Note: Examples of complement inhibitors are Soliris (eculizumab intravenous infusion), Ultomiris (ravulizumab-cwvz intravenou infusion or subcutaneous injection), and Zilbrysq (zilucoplan subcutaneous injection).

71.

265. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Northera Prior Authorization Policy
- Northera® (droxidopa capsules – Lundbeck)

REVIEW DATE: 12/13/2023

OVERVIEW

Northera, a norepinephrine-type product, is indicated for the treatment of orthostatic dizziness, lightheadedness, or the "feeling that one is about to black out" in adults with symptomatic **neurogenic orthostatic hypotension (NOH)** caused by primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy.[1]

Disease Overview

Orthostatic hypotension (OH) is a sustained reduction in systolic blood pressure (SBP) of at least 20 mmHg or diastolic blood pressure (DBP) of 10 mmHg within 3 minutes of standing or head-up tilt to at least 60° on a tilt table.[2] OH may be symptomatic or asymptomatic, with only symptomatic OH requiring treatment. NOH is a specific subset of this condition, in which OH is due to inadequate release of norepinephrine from sympathetic vasomotor neurons leading to vasoconstrictor failure. NOH is a rare, chronic and often debilitating condition that is associated with Parkinson's disease, multiple system atrophy, and pure autonomic failure, and with peripheral neuropathies and ganglionopathies that affect the autonomic nerves.[2-4] Symptoms of NOH include dizziness, lightheadedness, blurred vision, fatigue, and fainting upon standing up. These symptoms can adversely affect patients' quality of life and ability to conduct activities of daily living that involve standing or walking. Treatment of symptomatic NOH is aimed at increasing standing systolic blood pressure into the range of compensatory cerebrovascular autoregulation (approximately 50 to 150 mmHg).[5] Unapproved pharmacologic agents include fludrocortisone, dihydroergotamine (oral), indomethacin (oral or intravenous), pyridostigmine, and atomoxetine.[2-4,6] Midodrine, an alpha$_1$-agonist, is the only other medication approved with a similar indication (treatment of symptomatic orthostatic hypotension) to Northera.[7]

Guidelines

Consensus panel recommendations initiated by the American Autonomic Society and the National Parkinson Foundation for the screening, diagnosis, and treatment of NOH and associated supine hypertension were published in 2017.[8] Once a patient is diagnosed with NOH, the goals of treatment should be to reduce the burden of symptoms (especially falls), prolong standing time, and restore independence in activities of daily living. The recommendations propose a four-step treatment algorithm for NOH: assessing and adjusting preexisting medications that may be causing or exacerbating NOH, utilizing non-pharmacologic approaches (e.g., blood volume repletion, increased salt intake, physical conditioning, compression garments, elevating the head of the bed), implementing single-agent pharmacologic treatment, and with great caution, combining pharmacologic treatments. Recommended treatments include midodrine, Northera, fludrocortisone, and pyridostigmine. The initial choice of NOH treatments should be individualized and should consider severity, comorbid disease (especially cardiac or renal failure), and treatment goals. Based on the experience of the consensus panel, the recommendation is to titrate to maximum tolerable dose of a single medication and then, if symptomatic benefit is not obtained, consider switching to a different medication or adding a second agent and titrate from its lowest starting dose.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Northera. Because of the specialized skills required for evaluation and diagnosis of patients treated with Northera as well as the monitoring required for adverse events and long-term efficacy, approval requires Northera to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Northera is recommended in those who meet the following criteria:

FDA-Approved Indication

60. Neurogenic Orthostatic Hypotension. Approve for 1 year if the patient meets the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has been diagnosed with symptomatic neurogenic orthostatic hypotension due to primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, or non-diabetic autonomic neuropathy; AND
- **C)** Patient has tried two other medications; AND
  Note: Examples of other medications include atomoxetine, dihydroergotamine, fludrocortisone, indomethacin, midodrine, and pyridostigmine.
- **D)** Patient has initiated non-pharmacological measures including but not limited to elevation of the head of the bed, orthostatic compression garments, and appropriate physical training; AND
- **E)** The medication has been prescribed by or in consultation with a cardiologist or a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Northera is not recommended in the following situations:

133. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Nuedexta Prior Authorization Policy
- Nuedexta® (dextromethorphan hydrobromide and quinidine sulfate capsules – Avanir)

REVIEW DATE: 09/13/2023

OVERVIEW

Nuedexta, a combination product containing dextromethorphan hydrobromide (DM) and quinidine sulfate, is indicated for the **treatment of pseudobulbar affect**.[1]

The need for continued treatment should be reassessed periodically, as spontaneous improvement of pseudobulbar affect occurs in some patients.[1]

Disease Overview

Pseudobulbar affect is a neurologic condition characterized by involuntary outbursts of laughing and/or crying incongruous or disproportionate to the patients' emotional state.[2,7] There are many terms that have been used to describe this condition, including pathological laughing and crying, affective lability, emotional incontinence, emotionalism, and involuntary emotional expression disorder.[7] Pseudobulbar affect, hypothesized to arise from disconnection of brainstem structures from cortical inhibition, is associated with underlying central nervous system disorders including stroke, traumatic brain injury, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS).[2] In addition to the effects of the underlying disorder, pseudobulbar affect can have a severe impact on well-being and social functioning and can be highly disabling, owing in part to the stigma attached to loss of emotional control. Episodes of laughing can also lead to respiratory compromise, especially in patients with a neurological disorder that already compromises respiratory function, such as ALS.[7] For these reasons, treatment should be strongly considered in any patient with pseudobulbar affect. The goal of therapy is to reduce the frequency of attacks.

Clinical Efficacy

The efficacy of Nuedexta was established in one trial in patients with pseudobulbar affect with underlying ALS or MS.[1,2] Two additional trials conducted with higher doses (DM 30 mg/quinidine 30 mg) provided supportive evidence.[3,4] PRISM II, an open-label, 90-day, published study, evaluated Nuedexta in patients with pseudobulbar affect and a diagnosis of dementia, stroke, or traumatic brain injury (n = 367).[8] Nuedexta was shown to be an effective treatment for pseudobulbar affect secondary to dementia, stroke, or traumatic brain injury, showing similar improvement to that reported in patients with pseudobulbar affect secondary to ALS or MS.

Guidelines

There are no guidelines specific to the management of pseudobulbar affect. However, the American Academy of Neurology (AAN) published an evidence-based guideline on the assessment and management of psychiatric disorders in individuals with MS (reaffirmed 2019).[5] The guideline found that Nuedexta is possibly effective and may be considered for treating individuals with MS with pseudobulbar affect (Level C, one Class II study). Also, prior to the approval of Nuedexta, the AAN published a practice parameter on the care of the patient with ALS (reaffirmed 2023).[6] With regard to pharmacologic measures to reduce pseudobulbar affect, the AAN concludes that the combination DM/quinidine product is probably effective for pseudobulbar affect in ALS based on one Class I study[3], although side effects may limit its usefulness. Therefore, the AAN recommends that if approved by the FDA, and if side effects are acceptable, the

combination DM/quinidine product should be considered for symptoms of pseudobulbar affect in patients with ALS (Level B). No other pharmacologic agents are addressed in the practice parameter for use in the management of pseudobulbar affect.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Nuedexta. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nuedexta as well as the monitoring required for adverse events and long-term efficacy, approval requires Nuedexta to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nuedexta is recommended in those who meet the following criteria:

FDA-Approved Indication

2. **Treatment of Pseudobulbar Affect.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient has pseudobulbar affect associated with a chronic neurological condition; AND
   Note: Examples of chronic neurological conditions include amyotrophic lateral sclerosis, multiple sclerosis, stroke, dementia, traumatic brain injury.
   B) Nuedexta is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nuedexta is not recommended in the following situations:

1. **Heroin Detoxification.** Limited published data are available in patients undergoing heroin detoxification.[9] The available study was conducted with the DM 30 mg/quinidine 30 mg formulation, using daily doses of DM 60 mg/quinidine 60 mg (dose cannot be achieved with Nuedexta capsules). There were no differences between DM/quinidine and placebo with regard to reducing opioid withdrawal symptoms.

2. **Levodopa-Induced Dyskinesia in Parkinson's Disease.** A single pilot study demonstrated benefit with dextromethorphan/quinidine for treating levodopa-induced dyskinesia in Parkinson's disease.[12] Larger studies with a longer treatment duration are needed to define the place in therapy for Nuedexta in this condition.

3. **Neuropathic Pain.** Limited published data are available in patients (n = 36) with diabetic peripheral neuropathic (DPN) pain (open-label tolerability study).[10] The available study was conducted with the DM 30 mg/quinidine 30 mg formulation, using daily doses up to DM 120 mg/quinidine 120 mg (dose cannot be achieved with Nuedexta capsules). Higher daily doses of DM and quinidine (60 mg/60 mg and 90 mg/60 mg [doses cannot be achieved with Nuedexta capsules]) have also been evaluated in patients with DPN pain (n = 379) in one Phase III, randomized, placebo-controlled 13-week study.[7] Both DM/quinidine treatment groups had significant reductions in mean daily pain scores vs. placebo. More data are needed to define the place in therapy of Nuedexta in the treatment of neuropathic pain.

4. **Psychosis-Related Aggression**. A case series (n = 4) supports DM/quinidine as a potential alternative to conventional regimens for treating aggression and impulsive behavior in patients with psychotic disorder.[11] More data are needed to define the place in therapy of Nuedexta in the treatment of psychosis-related aggression.

5. **Treatment-Resistant Depression.** A Phase II, open-label, proof-of-concept study (n = 20) demonstrated preliminary efficacy for DM 45 mg/quinidine 10 mg every 12 hours. This dosing could not be achieved with Nuedexta capsules.[13] Additional data are needed to define the place in therapy for Nuedexta in the treatment of treatment-resistant depression.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

416. Nuedexta® capsules [prescribing information]. Aliso Viejo, CA: Avanir; December 2022.
417. Pioro EP, Brooks BR, Cummings J, et al. Dextromethorphan plus ultra low-dose quinidine reduces pseudobulbar affect. *Ann Neurol*. 2010;68:693-702.
418. Brooks BR, Thisted RA, Appel SH. Treatment of pseudobulbar affect in ALS with dextromethorphan/quinidine. *Neurology*. 2004;63:1364-1370.
419. Panitch HS, Thisted RA, Smith RA. Randomized, controlled trial of dextromethorphan/quinidine for pseudobulbar affect in multiple sclerosis. *Ann Neurol*. 2006;59:780-787.
420. Minden SL, Feinstein A, Kalb RC, et al. Evidence-based guideline: Assessment and management of psychiatric disorders in individuals with MS: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2014;82:174-181.
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422. Shaibani AI, Pope LE, Thisted R, Hepner A. Efficacy and safety of dextromethorphan/quinidine at two dosage levels for diabetic neuropathic pain: a double-blind, placebo-controlled, multicenter study. *Pain Med*. 2012;13:243-254.
423. Hammond FM, Alexander DN, Cutler AJ, et al. PRISM II: an open-label study to assess effectiveness of dextromethorphan/quinidine for pseudobulbar affect in patients with dementia, stroke or traumatic brain injury. *BMC Neurology*. 2016;16:89.
424. Akerele E, Bisaga A, Sullivan MA, et al. Dextromethorphan and quinidine combination for heroin detoxification. Am J Addict. 2008;17:176-180.
425. Thisted RA, Klaff L, Schwartz SL, et al. Dextromethorphan and quinidine in adult patients with uncontrolled painful diabetic peripheral neuropathy: a 29-day, multicenter, open-label, dose-escalation study. *Clin Ther*. 2006;28:1607-1618.
426. Chen Q, Calcagno HE, Shad M. Efficacy of dextromethorphan/quinidine for patients with psychosis-related aggression: a retrospective case series. *Prim Care Companion CNS Disord*. 2018;20(3).
427. Fox SH, Metman LV, Nutt JG, et al. Trial of dextromethorphan/quinidine to treat levodopa-induced dyskinesia in Parkinson's disease. *Mov Disord*. 2017;32(6):893-903.
428. Murrough JW, Wade E, Sayed S, et al. Dextromethorphan/quinidine pharmacotherapy in patients with treatment resistant depression: A proof of concept clinical trial. *J Affect Disord*. 2017;218:277-283.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable – CAR-T) – Abecma Prior Authorization Policy
- Abecma® (idecabtagene vicleucel intravenous infusion – Bristol-Myers Squibb and bluebird bio)

REVIEW DATE: 03/29/2023

OVERVIEW

Abecma, a B-cell maturation antigen (BCMA)-directed genetically modified autologous T-cell immunotherapy, is indicated for the treatment of adults with relapsed or refractory **multiple myeloma** after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.[1] Abecma is a chimeric antigen receptor T-cell (CAR-T) therapy.

Abecma is supplied in one or more frozen infusion bags contain a suspension of genetically modified autologous chimeric antigen receptor (CAR)-positive T-cells in 5% dimethyl sulfoxide.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for multiple myeloma (version 3.2023 – December 8, 2022) recommend Abecma for the treatment of previously treated multiple myeloma after at least four prior treatment regimens.[2,3] Patients should receive a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody before receiving Abecma.

Safety

Abecma has a Boxed Warning for cytokine release syndrome, neurologic toxicity, hemophagocytic lymphohistiocytosis/macrophage activation syndrome, and prolonged cytopenias.[1] Abecma is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called Abecma REMS.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Abecma. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Abecma as well as the monitoring required for adverse events and long-term efficacy, approval requires Abecma to be prescribed by or in consultation with a physician who specializes in the condition being treated. The approval duration is 6 months to allow for an adequate time frame to prepare and administer 1 dose of therapy.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Abecma is recommended in those who meet the following criteria:

FDA-Approved Indication

167. Multiple Myeloma. Approve a single dose if the patient meets the following criteria (A, B, C, D, and E):

A) Patient is ≥ 18 years of age; AND

B) Patient has received four or more lines of systemic therapy, including one from each of the following (i, ii, and iii):

i. Patient has received an immunomodulatory agent; AND
Note: Immunomodulatory agents include Thalomid (thalidomide capsules), lenalidomide capsules, Pomalyst (pomalidomide capsules).

ii. Patient has received a proteasome inhibitor; AND
Note: Proteasome inhibitors include bortezomib injection, Kyprolis (carfilzomib intravenous infusion), Ninlaro (ixazomib capsules).

iii. Patient has received an anti-CD38 monoclonal antibody; AND
Note: Anti-CD38 monoclonal antibodies include Darzalex (daratumumab intravenous infusion), Darzalex Faspro (daratumumab and hyaluronidase-fihj subcutaneous injection), Sarclisa (isatuximab-irfc intravenous infusion).

C) Patient has received or plans to receive lymphodepleting chemotherapy prior to infusion of Abecma; AND

D) Patient has not been previously treated with chimeric antigen receptor T-cell (CAR-T) therapy; AND
Note: Examples of CAR-T therapy includes Abecma, Carvykti (ciltacabtagene autoleucel intravenous infusion), Breyanzi (lisocabtagene maraleucel intravenous infusion), Kymriah (tisagenlecleucel intravenous infusion), Tecartus (brexucabtagene intravenous infusion), and Yescarta (axicabtagene intravenous infusion).

E) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Abecma is not recommended in the following situations:

266. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

810. Abecma intravenous infusion [prescribing information]. Summit, NJ: Bristol-Myers Squibb; March 2021.
811. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 3.2023 – December 8, 2022). © 2022 National Comprehensive Cancer Network, Available at: http://www.nccn.org. Accessed on March 20, 2023.
812. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 20, 2023. Search term: idecabtagene.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable – CAR-T) – Breyanzi Prior Authorization Policy
- Breyanzi® (lisocabtagene maraleucel intravenous infusion – Juno Therapeutics)

REVIEW DATE: 01/18/2023

OVERVIEW

Breyanzi, a CD19-directed genetically modified autologous T-cell immunotherapy, is indicated for the treatment of adults with **large B-cell lymphoma** including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B, who have:[1]

- Refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy.
- Refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation due to age or comorbidities.
- Relapsed or refractory disease after ≥ 2 lines of systemic therapy.

Limitations of use: Breyanzi is not indicated for the treatment of patients with primary central nervous system lymphoma.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines address Breyanzi:

- **B-Cell Lymphomas** (version 5.2022 – July 12, 2022) guidelines recommend Breyanzi for the treatment of a variety of lymphomas.[2,3] Breyanzi can be used as second-line and subsequent therapy for relapsed or refractory DLBCL, high-grade B-cell lymphoma, acquired immunodeficiency syndrome (AIDS)-related B-cell lymphoma, and post-transplant lymphoproliferative disorders. Breyanzi can also be used as third-line and subsequent therapy for transformed indolent lymphoma to DLBCL.
- **Pediatric Aggressive Mature B-Cell Lymphomas** (version 3.2022 – October 19, 2022) guidelines recommend Breyanzi for consolidation/additional therapy if the patient has achieved a partial response after treatment for relapsed/refractory primary mediastinal large B-cell lymphoma.[3,4] NCCN states this recommendation is based on extrapolation of results from clinical trials in adults with relapsed/refractory DLBCL including primary mediastinal large B-cell lymphoma.

Safety

Breyanzi has a Boxed Warning regarding cytokine release syndrome (CRS) and neurologic toxicities.[1] Breyanzi is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Breyanzi REMS.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Breyanzi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Breyanzi as well as the monitoring required for adverse events and long-term efficacy, approval requires Breyanzi to be prescribed by or in consultation with a physician who

specializes in the condition being treated. The approval duration is 6 months to allow for an adequate time frame to prepare and administer 1 dose of therapy.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Breyanzi is recommended in those who meet the following criteria:

FDA-Approved Indication

168. B-Cell Lymphoma. Approve a single dose if the patient meets ALL of the following criteria (A, B, C, D, and E):

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following (i or ii):
  - **i.** Patient meets BOTH of the following (a and b):
    - **a)** Patient has ONE of the following diagnoses [(1), (2), (3), (4), (5), (6), (7), (8), or (9)]:
      - **(1)** Large B-cell lymphoma; OR
      - **(2)** Diffuse large B-cell lymphoma; OR
      - **(3)** High-grade B-cell lymphoma; OR
      - **(4)** Primary mediastinal large B-cell lymphoma; OR
      - **(5)** Follicular lymphoma, Grade 3B; OR
      - **(6)** Acquired immunodeficiency syndrome (AIDS)-related diffuse large B-cell lymphoma; OR
      - **(7)** Human herpesvirus-8 (HHV8)-positive diffuse large B-cell lymphoma; OR
      - **(8)** Primary effusion lymphoma; OR
      - **(9)** Post-transplant lymphoproliferative disorders; AND
    - **b)** Patient has received at least one line of systemic therapy; OR
  - **ii.** Patient meets BOTH of the following (a and b):
    - **a)** Patient has transformed indolent lymphoma to diffuse large B-cell lymphoma; AND
    - **b)** Patient has received at least two lines of systemic therapy; AND
- **C)** Patient has received or plan to receive lymphodepleting chemotherapy prior to infusion of Breyanzi; AND
- **D)** Patient has not been previously treated with CAR-T therapy; AND
  Note: Examples of CAR-T therapy includes Breyanzi, Kymriah (tisagenlecleucel intravenous infusion), Tecartus (brexucabtagene intravenous infusion), and Yescarta (axicabtagene intravenous infusion).
- **E)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Breyanzi is not recommended in the following situations:

267. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

813. Breyanzi® intravenous infusion [prescribing information]. Bothell, WA: Juno Therapeutics; June 2022.
814. The NCCN B-Cell Lymphoma Clinical Practice Guidelines in Oncology (version 5.2022 – July 12, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed January 17, 2023.

815. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 17, 2023. Search term: lisocabtagene.
816. The NCCN Pediatric Aggressive Mature B-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 3.2022 – October 19, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed January 17, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable – CAR-T) – Carvykti Prior Authorization Policy
- Carvykti® (ciltacabtagene autoleucel intravenous infusion – Janssen Biotech)

REVIEW DATE: 03/22/2023

OVERVIEW

Carvykti, a B-cell maturation antigen (BCMA)-directed genetically modified autologous T-cell immunotherapy, is indicated for the treatment of adults with relapsed or refractory **multiple myeloma**, after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.[1]

Carvykti is supplied in one infusion bag containing a frozen suspension of genetically modified autologous T-cells in 5% dimethyl sulfoxide.[1] The bag is stored in the vapor phase of liquid nitrogen (-184°F).

Guidelines

The National Comprehensive Cancer Network clinical practice guidelines for multiple myeloma (version 3.2023 – December 8, 2022) recommend Carvykti for the treatment of multiple myeloma in patients who have received four or more previous therapies.[2,3] Patients should receive a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody before receiving Carvykti.

Safety

Carvykti has a boxed warning for cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, parkinsonism and Guillain-Barre syndrome, hemophagocytic lymphohistiocytosis/macrophage activation syndrome, and prolonged and/or recurrent cytopenias.[1] Carvykti is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Carvykti REMS.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Carvykti. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Carvykti as well as the monitoring required for adverse events and long-term efficacy, approval requires Carvykti to be prescribed by or in consultation with a physician who specializes in the condition being treated. The approval duration is 6 months to allow for an adequate time frame to prepare and administer 1 dose of therapy.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Carvykti is recommended in those who meet the following criteria:

FDA-Approved Indication

169. Multiple Myeloma. Approve a single dose if the patient meets the following criteria (A, B, C, D, and E):

A) Patient is ≥ 18 years of age; AND

B) Patient has received four or more lines of systemic therapy, including one from each of the following (i, ii, and iii):

i. Immunomodulatory agent; AND
Note: Immunomodulatory agents include Thalomid (thalidomide capsules), lenalidomide capsules, and Pomalyst (pomalidomide capsules).

ii. Proteasome inhibitor; AND
Note: Proteasome inhibitors include bortezomib injection, Kyprolis (carfilzomib intravenous infusion), and Ninlaro (ixazomib capsules).

iii. Anti-CD38 monoclonal antibody; AND
Note: Anti-CD38 monoclonal antibodies include Darzalex (daratumumab intravenous infusion), Darzalex Faspro (daratumumab and hyaluronidase-fihj subcutaneous injection), and Sarclisa (isatuximab-irfc intravenous infusion).

C) Patient has received or plans to receive lymphodepleting chemotherapy prior to infusion of Carvykti; AND

D) Patient has not been previously treated with chimeric antigen receptor (CAR-T) therapy; AND
Note: Examples of CAR-T therapy includes Carvykti, Abecma (idecabtagene vicleucel intravenous infusion), Breyanzi (lisocabtagene maraleucel intravenous infusion), Kymriah (tisagenlecleucel intravenous infusion), Tecartus (brexucabtagene intravenous infusion), and Yescarta (axicabtagene intravenous infusion).

E) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Carvykti is not recommended in the following situations:

268. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

817. Carvykti intravenous infusion [prescribing information]. Horsham, PA: Janssen Biotech; February 2023.
818. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 8, 2023.
819. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 3.2023 – December 8, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 8, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable – CAR-T) – Kymriah Prior Authorization Policy
- Kymriah® (tisagenlecleucel intravenous infusion – Novartis Oncology)

REVIEW DATE: 03/29/2023

OVERVIEW

Kymriah, a CD19-directed genetically modified autologous T cell immunotherapy, is indicated for the following uses:[1]

- **B-cell precursor acute lymphoblastic leukemia** (ALL), in patients ≤ 25 years of age with disease that is refractory or in second or later relapse.
- **Follicular lymphoma**, in patients ≥ 18 years of age with relapsed or refractory disease after two or more lines of systemic therapy. This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).
- **Large B-cell lymphoma**, in patients ≥ 18 years of age with relapsed or refractory disease after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
  Limitation of Use: Kymriah is not indicated for treatment of patients with primary central nervous system lymphoma.

Kymriah, a chimeric antigen receptor T-cell (CAR-T) therapy, is supplied as a frozen suspension of genetically modified autologous T cells in infusion bag(s) labeled for the specific recipient.[1] Kymriah is shipped directly to the cell laboratory associated with the infusion center in a liquid nitrogen Dewar. The product and patient-specific labels are found inside the Dewar. Store the infusion bag in the vapor phase of liquid nitrogen (less than or equal to minus 120°C) in a temperature-monitored system. Kymriah should be thawed prior to infusion.

Guidelines

Kymriah is discussed in guidelines from The National Comprehensive Cancer Network (NCCN).

- **ALL, adult:** The NCCN guidelines (version 1.2022 – April 4, 2022) address Kymriah.[2,3] In Philadelphia chromosome-positive B-cell ALL, Kymriah is cited as a treatment option for patients < 26 years of age and with refractory disease or ≥ two relapses and failure of two tyrosine kinase inhibitors (TKIs) [category 2A]. For Philadelphia chromosome-negative B-cell ALL, Kymriah is listed as a therapy option for patients < 26 years of age and with refractory disease or ≥ two relapses (category 2A).
- **ALL, pediatric:** The NCCN guidelines (version 2.2023 – March 10, 2023) recommend Kymriah for the treatment of patients with refractory or ≥ two relapses, TKI intolerant or refractory disease, or relapse post-hematopoietic stem cell transplantation (category 2A).[3,5] Kymriah is also recommended for patients who are minimal residual disease positive after consolidation therapy, and in Philadelphia chromosome-positive disease with less than complete response.
- **B-cell lymphoma:** The NCCN guidelines (version 2.2023 – February 8, 2023) recommend Kymriah for the treatment of the following relapsed or refractory disease after at least two course of systemic therapy: DLBCL, DLBCL following transformation from follicular lymphoma or nodal marginal zone lymphoma, follicular lymphoma, high-grade B-cell lymphoma, human immunodeficiency virus (HIV)-related B-cell lymphoma, human herpes virus 8 (HHV8)-positive

DLBCL, primary effusion lymphoma, and post-transplant lymphoproliferative disorders (category 2A).[3,4]

Safety
Kymriah has a Boxed Warning regarding cytokine release syndrome and neurological toxicities.[1] Due to these risks, Kymriah is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Kymriah REMS.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Kymriah. All approvals for therapy are provided for the approval duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kymriah as well as the monitoring required for adverse events and long-term efficacy, approval requires Kymriah to be prescribed by or in consultation with a physician who specializes in the condition being treated. The approval duration is 6 months to allow for an adequate time frame to prepare and administer 1 dose of therapy.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Kymriah is recommended in those who meet one of the following criteria:

FDA-Approved Indications

170. Acute Lymphoblastic Leukemia, B-Cell Precursor. Approve a single dose if the patient meets the following criteria (A, B, C, D, and E):
- **A)** Patient is < 26 years of age; AND
- **B)** Patient meets one of the following (i, ii, or iii):
  - **i.** Patient has disease that is refractory, or in second or later relapse; OR
  - **ii.** Patient is minimal residual disease positive after consolidation therapy; OR
  - **iii.** Patient is Philadelphia chromosome-positive and has experienced one of the following (a, b, or c):
    - **a)** Less than complete response; OR
    - **b)** Tyrosine kinase inhibitor intolerant or refractory disease; OR
      Note: Tyrosine kinase inhibitors include Sprycel (dasatinib tablets), imatinib tablets, Iclusig (ponatinib tablets), Tasigna (nilotinib capsules), and Bosulif (bosutinib tablets).
    - **c)** Relapse post-hematopoietic stem cell transplantation; AND
- **C)** Patient received or plans to receive lymphodepleting chemotherapy prior to Kymriah infusion; AND
- **D)** Patient has not been previously treated with chimeric antigen receptor T-cell (CAR-T) therapy; AND
  Note: Examples of CAR-T therapy includes Kymriah, Breyanzi (lisocabtagene maraleucel intravenous infusion), Tecartus (brexucabtagene autoleucel intravenous infusion), Yescarta (axicabtagene ciloleucel intravenous infusion), Abecma (idecabtagene vicleucel intravenous infusion) and Carvykti (ciltacabtagene autoleuleucel intravenous infusion).
- **E)** Kymriah is prescribed by or in consultation with an oncologist.

2. **B-Cell Lymphoma.** Approve a single dose if the patient meets the following criteria (A, B, C, D, E, and F):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has one of the following diagnoses (i, ii, iii, iv, v, vi, vii, viii, ix, or x):
     - **i.** Large B-cell lymphoma; OR
     - **ii.** Diffuse large B-cell lymphoma; OR
     - **iii.** Diffuse large B-cell lymphoma arising from follicular lymphoma; OR
     - **iv.** Diffuse large B-cell lymphoma arising from nodal marginal zone lymphoma; OR
     - **v.** Follicular lymphoma; OR
     - **vi.** High-grade B-cell lymphoma; OR
     - **vii.** Human immunodeficiency virus (HIV)-related B-cell lymphoma; OR
     - **viii.** Human Herpes Virus 8-positive diffuse large B-cell lymphoma; OR
     - **ix.** Primary effusion lymphoma; OR
     - **x.** Post-transplant lymphoproliferative disorders, B-cell type; AND
   - **C)** Kymriah is being used for disease that is relapsed or refractory after two or more lines of systemic therapy; AND
   - **D)** Patient meets one of the following (i or ii):
     - **i.** Patient received or plans to receive lymphodepleting chemotherapy prior to Kymriah infusion; OR
     - **ii.** Patient's white blood cell count is less than or equal to 1 x 10^9/L within 1 week prior to Kymriah infusion; AND
   - **E)** Patient has not been previously treated with chimeric antigen receptor T-cell (CAR-T) therapy; AND

     Note: Examples of CAR-T therapy includes Kymriah, Breyanzi (lisocabtagene maraleucel intravenous infusion), Tecartus (brexucabtagene autoleucel intravenous infusion), Yescarta (axicabtagene ciloleucel intravenous infusion), Abecma (idecabtagene vicleucel intravenous infusion), and Carvykti (ciltacabtagene autoleucel intravenous infusion).
   - **F)** Kymriah is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kymriah is not recommended in the following situations:

269. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

820. Kymriah™ intravenous infusion [prescribing information]. East Hanover, NJ: Novartis Oncology; May 2022.
821. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 1.2022 – April 4, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 20, 2023.
822. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 20, 2023. Search term: tisagenlecleucel.
823. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 2.2023 – February 8, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 20, 2023.
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PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable – CAR-T) – Tecartus Prior Authorization Policy
- Tecartus® (brexucabtagene autoleucel intravenous infusion – Kite Pharma)

REVIEW DATE: 08/16/2023

OVERVIEW

Tecartus, a CD19-directed genetically modified autologous T cell immunotherapy, is indicated for the treatment of adults with relapsed or refractory:[1]

- **B-cell precursor acute lymphoblastic leukemia**.
- **Mantle cell lymphoma**.

Tecartus is supplied in infusion bag(s) containing frozen suspension of genetically modified autologous T cells in human serum albumin.[1] Each bag is supplied in a metal cassette stored in the vapor phase of liquid nitrogen. Store Tecartus frozen in the vapor phase of liquid nitrogen and thaw prior to administration.

Guidelines

Tecartus is addressed in National Comprehensive Cancer Network guidelines:

- **Acute lymphoblastic leukemia:** Guidelines (version 2.2023 – July 28, 2023) recommend Tecartus for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia.[3,4]
- **B-cell lymphomas:** Guidelines (version 5.2023 – July 7, 2023) recommend Tecartus for the third-line treatment of relapsed or refractory mantle cell lymphoma, following treatment with chemoimmunotherapy and Bruton tyrosine kinase inhibitor therapy.[2,3]

Safety

Tecartus has a Boxed Warning regarding cytokine release syndrome and neurological toxicities. Due to these risks, Tecartus is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Tecartus REMS.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tecartus. All approvals for therapy are provided for the approval duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tecartus as well as the monitoring required for adverse events and long-term efficacy, approval requires Tecartus to be prescribed by or in consultation with a physician who specializes in the condition being treated. The approval duration is 6 months to allow for an adequate time frame to prepare and administer 1 dose of therapy.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tecartus is recommended in those who meet one of the following criteria:

FDA-Approved Indications

171. Acute Lymphoblastic Leukemia. Approve a single dose if the patient meets all of the following (A, B, C, D, E, and F):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has B-cell precursor disease; AND
- **C)** Patient has relapsed or refractory disease; AND
- **D)** Patient received or plans to receive lymphodepleting chemotherapy prior to Tecartus infusion; AND
- **E)** Patient has not been previously treated with CAR-T therapy; AND
  Note: Examples of CAR-T therapy include Tecartus, Breyanzi (lisocabtagene maraleucel intravenous infusion), Kymriah (tisagenlecleucel intravenous infusion), Yescarta (axicabtagene intravenous infusion) and Abecma (idecabtagene vicleucel intravenous infusion).
- **F)** Tecartus is prescribed by or in consultation with an oncologist.

172. Mantle Cell Lymphoma. Approve a single dose if the patient meets all of the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has previously received the following (i and ii):
  - **i.** Chemoimmunotherapy; AND
    Note: Examples of chemoimmunotherapy include bendamustine + rituximab, DHAP (dexamethasone, cisplatin, cytarabine) + rituximab, DHAX (dexamethasone, cytarabine, oxaliplatin) + rituximab.
  - **ii.** A Bruton tyrosine kinase inhibitor; AND
    Note: Bruton tyrosine kinase inhibitors include Brukinsa (zanubrutinib capsules), Calquence (acalabrutinib capsules), and Imbruvica (ibrutinib capsules and tablets).
- **C)** Patient received or plans to receive lymphodepleting chemotherapy prior to Tecartus infusion; AND
- **D)** Patient has not been previously treated with CAR-T therapy; AND
  Note: Examples of CAR-T therapy include Tecartus, Breyanzi (lisocabtagene maraleucel intravenous infusion), Kymriah (tisagenlecleucel intravenous infusion), Yescarta (axicabtagene intravenous infusion) and Abecma (idecabtagene vicleucel intravenous infusion).
- **E)** Tecartus is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tecartus is not recommended in the following situations:

270. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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827. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on August 11, 2023. Search term: brexucabtagene.
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PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable – CAR-T) – Yescarta Prior Authorization Policy
- Yescarta® (axicabtagene ciloleucel intravenous infusion – Kite Pharma)

REVIEW DATE: 03/29/2023

OVERVIEW

Yescarta, a CD19-directed genetically modified autologous T cell immunotherapy, is indicated for the treatment of adults with:[1]

- **Follicular lymphoma** that has relapsed or is refractory after two or more lines of systemic therapy. This indication was approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).
- **Large B-cell lymphoma** in the following situations:
  - Disease that is refractory to first-line chemoimmunotherapy or relapses within 12 months of first-line chemoimmunotherapy.
  - Relapsed or refractory disease after two or more lines of systemic therapy, including diffuse B-cell lymphoma (DLBCL) not otherwise specified, primarily mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
    Limitation of Use: Yescarta is not indicated for the treatment of patients with primary central nervous system lymphoma.

Yescarta, a chimeric antigen receptor T-cell (CAR-T) therapy, is supplied as an infusion bag containing approximately 68 mL of frozen suspension of genetically modified autologous T cells.[1] Yescarta is stored in the vapor phase of liquid nitrogen (less than or equal to minus 150°C) and supplied in a liquid nitrogen dry shipper.

Guidelines

The National Comprehensive Cancer Network (NCCN) has addressed Yescarta in the following guidelines:

- **B-cell lymphoma:** Guidelines (version 2.2023 – February 8, 2023) recommend Yescarta for the treatment of a variety of B-cell lymphomas in patients with relapsed or refractory disease and after at least two chemotherapy regimens.[2,3] Recommended indications include follicular lymphoma grade 1 or 2, extranodal marginal zone lymphoma of the stomach, extranodal marginal zone lymphoma of nongastric sites (noncutaneous), nodal marginal zone lymphoma, splenic marginal zone lymphoma, DLBCL, DLBCL which transformed from follicular lymphoma or nodal marginal zone lymphoma, high-grade B-cell lymphoma, human immunodeficiency virus (HIV)-related B-cell lymphoma, primary effusion lymphoma, human herpes virus 8 (HHV8)-positive DLBCL, and post-transplant lymphoproliferative disorders (category 2A). In addition, Yescarta is recommended for DLBCL, high-grade B-cell lymphoma, HIV-related B-cell lymphoma, primary effusion lymphoma, HHV8-positive DLBCL, and post-transplant lymphoproliferative disorders as additional therapy for relapsed or refractory disease > 12 months after completion of first-line therapy and partial response following second-line therapy (category 2A) and for patients with primary refractory or relapsed disease < 12 months after first-line therapy (category 1 for DLBCL, category 2A for all others).
- **Pediatric aggressive mature B-cell lymphoma:** Guidelines (version 3.2022 – October 19, 2022) recommend Yescarta for relapsed or refractory primary mediastinal large B-cell lymphoma after at least two chemotherapy regimens, as additional therapy for relapsed or refractory disease > 12

months after completion of first-line therapy and partial response following second-line therapy, and for patients with primary refractory or relapsed disease < 12 months after first-line therapy (category 2A).[3,4]

Safety
Yescarta has a Boxed Warning regarding cytokine release syndrome and neurological toxicities. Due to these risks, Yescarta is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called Yescarta REMS.[1]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Yescarta. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Yescarta as well as the monitoring required for adverse events and long-term efficacy, approval requires Yescarta to be prescribed by or in consultation with a physician who specializes in the condition being treated. The approval duration is 6 months to allow for an adequate time frame to prepare and administer 1 dose of therapy.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Yescarta is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **B-Cell Lymphoma.** Approve a single dose if the patient meets ALL of the following (A, B, C, D, and E):
   - **C)** Patient is ≥ 18 years of age; AND
   - **D)** Patient meets ONE of the following (i or ii):
     - **a)** Patient meets BOTH of the following (a and b):
       1. Patient has ONE of the following diagnoses [(1), (2), (3), (4), (5), (6), or (7)]:
          - **(1)** Follicular lymphoma; OR
          - **(2)** Extranodal marginal zone lymphoma of the stomach; OR
          - **(3)** Extranodal marginal zone lymphoma of nongastric sites (noncutaneous); OR
          - **(4)** Nodal marginal zone lymphoma; OR
          - **(5)** Splenic marginal zone lymphoma; OR
          - **(6)** Diffuse large B-cell lymphoma arising from follicular lymphoma; OR
          - **(7)** Diffuse large B-cell lymphoma arising from nodal marginal zone lymphoma; AND
     - **b)** Yescarta is used for disease that is relapsed or refractory after two or more lines of systemic therapy; OR
       Note: Examples of systemic therapy include CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + Gazyva (obinutuzumab intravenous infusion) or rituximab products, CVP (cyclophosphamide, vincristine, prednisone) + rituximab products, lenalidimide + rituximab products.
     - **ii.** Patient meets BOTH of the following (a and b):
       - **a)** Patient has ONE of the following diagnoses [(1), (2), (3), (4), (5), (6), (7), or (8)]:
         - **(1)** Human immunodeficiency virus (HIV)-related B-cell lymphoma; OR
         - **(2)** Human herpes virus 8-positive diffuse large B-cell lymphoma; OR
         - **(3)** Primary effusion lymphoma; OR

(4) Post-transplant lymphoproliferative disorders; OR
(5) Diffuse large B-cell lymphoma; OR
(6) Primary mediastinal large B-cell lymphoma; OR
(7) High-grade B-cell lymphoma; OR
(8) Large B-cell lymphoma; AND

b) Yescarta is used in ONE of the following situations [(1), (2), (3), or (4)]:
   a. Disease that is relapsed or refractory after two or more lines of systemic therapy; OR
      Note: Examples of systemic therapy include RCHOP (rituximab product, cyclophosphamide, doxorubicin, vincristine, prednisone), dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab product, DHA (dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) ± rituximab product.
   b. Primary refractory disease; OR
   c. Relapsed disease < 12 months after completion of first-line therapy; OR
      Note: Examples of first-line therapy include RCHOP (rituximab product, cyclophosphamide, doxorubicin, vincristine, prednisone), dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab product, RCDOP (rituximab product, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone).
   d. Disease relapse > 12 months after first-line therapy in a patient with intent to proceed to transplantation who has partial response to second-line therapy; AND
      Note: Examples of systemic therapy include RCHOP (rituximab product, cyclophosphamide, doxorubicin, vincristine, prednisone), dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab product, RCDOP (rituximab product, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone).

E) Patient received or plans to receive lymphodepleting chemotherapy prior to Yescarta infusion; AND

F) Patient has not been previously treated with chimeric antigen receptor T-cell (CAR-T) therapy; AND
   Note: Examples of CAR-T therapy includes Yescarta, Breyanzi (lisocabtagene maraleucel intravenous infusion), Kymriah (tisagenlecleucel intravenous infusion), Tecartus (brexucabtagene autoleucel intravenous infusion) Abecma (idecabtagene vicleucel intravenous infusion) and Carvykti (ciltacabtagene autoleucel intravenous infusion).

G) Yescarta is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Yescarta is not recommended in the following situations:

271. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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831. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 21, 2023. Search term: axicabtagene.

832. The NCCN Pediatric Aggressive Mature B-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 3.2022 – October 19, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 21, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable – Programmed Death Receptor-1) – Jemperli Prior Authorization Policy

- Jemperli™ (dostarlimab intravenous infusion – GlaxoSmithKline)

REVIEW DATE: 05/10/2023

OVERVIEW

Jemperli, a programmed death receptor-1 blocking antibody, is indicated for the treatment of adults withrecurrent or advanced:[1]

- **Endometrial cancer** that is mismatch repair deficient (dMMR) as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen in any setting and are not candidates for curative surgery or radiation, as a single agent.
- **Endometrial cancer** that is dMMR as determined by an FDA-approved test or microsatellite instability-high (MSI-H), in combination with carboplatin and paclitaxel, followed by Jemperli as a single agent.
- **Solid tumors**, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.

Guidelines

Jemperli is addressed in the National Comprehensive Cancer Network guidelines:*

- **Ampullary Adenocarcinoma:** Guidelines (version 1.2023 – April 27, 2023) recommend Jemperli as subsequent therapy for MSI-H/dMMR tumors in patients whose cancer has progressed on or following prior treatment and who have no satisfactory alternative treatment options.
- **Biliary Tract Cancer:** Guidelines (version 1.2023 – March 10, 2023) recommend Jemperli for the subsequent treatment of MSI-H/dMMR gallbladder cancer, intrahepatic cholangiocarcinoma, and extrahepatic cholangiocarcinoma in patients whose cancer has progressed on or following prior treatment and who have no satisfactory alternative treatment options (category 2B).[2,14]
- **Breast Cancer:** Guidelines (version 4.2023 – March 23, 2023) recommend Jemperli as subsequent therapy for MSI-H/dMMR tumors in patients whose cancer has progressed on or following prior treatment and who have no satisfactory alternative treatment options.[2,7]
- **Colon Cancer:** Guidelines (version 2.2023 – April 25, 2023) recommend Jemperli as neoadjuvant therapy for MSI-H/dMMR colon cancer, and primary or subsequent therapy for MSI-H/dMMR colon cancer or appendiceal adenocarcinoma.[2,11]
- **Esophageal and Esophagogastric Junction Cancers:** Guidelines (version 2.2023 – March 10, 2023) recommend Jemperli as subsequent therapy for MSI-H/dMMR tumors in patients whose cancer has progressed on or following prior treatment and who have no satisfactory alternative treatment options.[2,6]
- **Gastric Cancer:** Guidelines (version 1.2023 – March 10, 2023) recommend Jemperli as subsequent therapy for MSI-H/dMMR tumors in patients whose cancer has progressed on or following prior treatment and who have no satisfactory alternative treatment options.[2,5]
- **Hepatocellular Carcinoma:** Guidelines (version 1.2023 – March 10, 2023) recommend Jemperli for the subsequent treatment of MSI-H/dMMR hepatocellular carcinoma in patients whose cancer has progressed on or following prior treatment and who have no satisfactory alternative treatment options (category 2B).[2,10]

- **Occult Primary:** Guidelines (version 3.2023 – December 21, 2022) recommend Jemperli as a single agent for dMMR/MSI-H tumors in symptomatic patients with performance status of 1 or 2, or asymptomatic patients with performance status of 0, in a variety of solid tumors.[3,4]
- **Ovarian Cancer:** Guidelines (version 1.2023 – December 22, 2022) recommend Jemperli as subsequent therapy for MSI-H/dMMR epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer, carcinosarcoma, clear cell or mucinous carcinoma of the ovary, grade 1 endometrioid carcinoma, and low grade serous carcinoma in patients with recurrent or advanced tumors.[2,9]
- **Rectal Cancer:** Guidelines (version 2.2023 – April 25, 2023) recommend Jemperli as neoadjuvant, primary, or subsequent therapy for MSI-H/dMMR disease.[2,12]
- **Small Bowel Adenocarcinoma:** Guidelines (version 1.2023 – January 9, 2023) recommend Jemperli as initial therapy for MSI-H/dMMR disease in patients who received oxaliplatin in the adjuvant setting or have a contraindication to oxaliplatin.[2,13] Jemperli is recommended for the subsequent treatment of MSI-H/dMMR disease in patients with no prior adjuvant oxaliplatin use or a contraindication to oxaliplatin.
- **Uterine Neoplasms:** Guidelines (version 2.2023 – April 28, 2023) recommend Jemperli for primary or adjuvant treatment, and for first- and second-line treatment of advanced, recurrent, or metastatic endometrial carcinoma.[2,3]

*All are category 2A recommendations unless otherwise noted.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Jemperli. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Jemperli as well as the monitoring required for adverse events and long-term efficacy, approval requires Jemperli to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Jemperli is recommended in those who meet one of the following criteria:

FDA-Approved Indications

173. Endometrial Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has recurrent, advanced, or metastatic disease; AND
- **C)** The medication is prescribed by or in consultation with an oncologist.

174. Mismatch Repair Deficient (dMMR) or Microsatellite Instability-High (MSI-H) Solid Tumors. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
Note: Examples of solid tumors include ampullary adenocarcinoma, breast cancer, esophageal and esophagogastric junction cancer, gastric cancer, hepatobiliary cancer, and ovarian cancer.
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has progressed on or after prior treatment; AND

C) According to the prescriber, the patient does not have any satisfactory alternative treatment options; AND
D) The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

175. Colon, Rectal, or Appendiceal Cancer. Approve for the duration noted if the patient meets all of the following (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) disease; AND
C) Patient has advanced or metastatic disease; AND
D) Patient meets ONE of the following (i or ii):
i. Approve for 6 months total if medication used for neoadjuvant therapy; OR
ii. Approve for 1 year if medication is used for primary or subsequent therapy; AND
E) Medication is prescribed by or in consultation with an oncologist.

176. Small Bowel Adenocarcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) disease; AND
C) Patient has advanced or metastatic disease; AND
D) Patient meets ONE of the following (i or ii):
i. Patient meets BOTH of the following (a and b):
a) Jemperli will be used as initial therapy; AND
b) Patient meets ONE of the following [(1) or (2)]:
(1) Patient has received adjuvant oxaliplatin; OR
(2) Patient has a contraindication to oxaliplatin; OR
ii. Patient meets ALL of the following (a, b, and c):
a) Jemperli is used as subsequent therapy; AND
b) Patient has NOT received oxaliplatin in the adjuvant setting; AND
c) Patient does NOT have contraindications to oxaliplatin; AND
E) The medication is prescribed by or consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Jemperli is not recommended in the following situations:

272. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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834. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 2, 2023. Search term: dostarlimab.
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838. The NCCN Esophageal and Esophagogastric Junction Cancers Clinical Practice Guidelines in Oncology (version 2.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 2, 2023.
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840. The NCCN Ampullary Adenocarcinoma Clinical Practice Guidelines in Oncology (version 1.2023 – April 27, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 3, 2023.
841. The NCCN Ovarian Cancer including Fallopian Tube and Primary Peritoneal Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 2, 2023.
842. The NCCN Hepatocellular Carcinoma Clinical Practice Guidelines in Oncology (version 1.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 2, 2023.
843. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 3, 2023.
844. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 3, 2023.
845. The NCCN Small Bowel Adenocarcinoma Clinical Practice Guidelines in Oncology (version 1.2023 – January 9, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 2, 2023.
846. The NCCN Biliary Tract Cancers Clinical Practice Guidelines in Oncology (version 1.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 2, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable – Programmed Death Receptor-1) – Keytruda Prior Authorization Policy
- Keytruda® (pembrolizumab intravenous infusion – Merck)

REVIEW DATE: 04/26/2023

OVERVIEW

Keytruda, a human programmed death receptor-1 (PD-1) blocking antibody, is indicated for the treatment of the following indications:[1]

- **Breast cancer, triple-negative**, in the following situations:
  - In combination with chemotherapy for the treatment of locally recurrent unresectable or metastatic disease in patients whose tumors express programmed death-ligand 1 (PD-L1) [combined positive score {CPS} ≥ 10] as determined by an FDA-approved test.
  - For the treatment of high-risk, early-stage disease in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.
- **Cervical cancer**, in the following situations:
  - In combination with chemotherapy, with or without bevacizumab, for persistent, recurrent, or metastatic disease in patients whose tumor expresses PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.
  - As a single agent, for treatment of recurrent or metastatic disease with disease progression on or after chemotherapy in patients whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.
- **Classical Hodgkin lymphoma**, in the following situations:
  - For treatment of relapsed or refractory disease in adults.
  - For the treatment of refractory disease, or disease that has relapsed after two or more prior lines of therapy in pediatric patients.
- **Cutaneous squamous cell carcinoma,** for treatment of patients with recurrent, metastatic disease or locally advanced disease that is not curable by surgery or radiation.
- **Endometrial cancer**, in the following situations:
  - In combination with Lenvima® (lenvatinib capsules), for the treatment of advanced disease that is mismatch repair proficient (pdMMR) as determined by an FDA-approved test or not microsatellite instability high (MSA-H), in patients, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.
  - As a single agent, for the treatment of advanced disease that is MSI-H or mismatch repair deficient (dMMR) as determined by an FDA-approved test, in patients who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.
- **Esophageal cancer**, treatment of locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) carcinoma (tumors with epicenter 1 to 5 centimeters above the GEJ) that is not amenable to surgical resection or definitive chemoradiation in the following situations:
  - In combination with platinum- and fluoropyrimidine-based chemotherapy.
  - As a single agent after one or more prior lines of systemic therapy for tumors of squamous cell histology that express PD-L1 (CPS ≥ 10) as determined by an FDA-approved test.
- **Gastric cancer**, for the first-line treatment of locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive gastric or GEJ adenocarcinoma, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy.*

- **Head and neck squamous cell carcinoma**, in the following situations:
  - As a single agent for the treatment of recurrent or metastatic disease with disease progression on or after platinum-containing chemotherapy.
  - In combination with platinum and fluorouracil (FU) for the first-line treatment of metastatic or with unresectable, recurrent disease.
  - As a single agent, for the first line treatment of metastatic or unresectable, recurrent disease in patients whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.
- **Hepatocellular carcinoma**, for treatment of hepatocellular carcinoma in patients who have been previously treated with Nexavar® (sorafenib tablets).*
- **Melanoma**, in the following situations:
  - For the treatment of unresectable or metastatic disease.
  - As adjuvant treatment of Stage IIB, IIC, or III melanoma following complete resection in patients ≥ 12 years of age.
- **Merkel cell carcinoma**, for treatment of recurrent, locally advanced, or metastatic disease in adults and pediatric patients.*
- **Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancer**, for treatment of unresectable or metastatic MSI-H or dMMR solid tumors, as determined by an FDA-approved test, in adult and pediatric patients that have progressed following prior treatment and who have no satisfactory alternative treatment options.
- **Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer,** for the treatment of unresectable or metastatic disease, as determined by an FDA-approved test.
- **Non-small cell lung cancer** (**NSCLC**), in the following situations:
  - As a single agent for the first-line treatment of tumors that express PD-L1 (tumor proportion score [TPS] ≥ 1%) as determined by an FDA-approved test, with no epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations, and is stage III where patients are not candidates for surgical resection or definitive chemoradiation or for metastatic disease.
  - As a single agent for the treatment of metastatic disease in patients whose tumors express PD-L1 (TPS ≥ 1%) as determined by an FDA-approved test and with disease progression on or after platinum-containing chemotherapy. Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Keytruda.
  - In combination with pemetrexed and platinum-based chemotherapy, for the first-line treatment of metastatic nonsquamous NSCLC in patients with no *EGFR* or *ALK* genomic tumor aberrations.
  - In combination with carboplatin and either paclitaxel or paclitaxel protein-bouns, for first-line treatment in metastatic squamous NSCLC.
  - As a single agent, as adjuvant treatment following resection and platinum-based chemotherapy for stage IB, II, or IIIA NSCLC in adults.
- **Primary mediastinal large B-cell lymphoma** (PMBCL), for treatment of refractory disease, or relapsed disease after two or more prior lines of therapy, in adults and pediatric patients.
  Limitation of Use: Keytruda is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.
- **Renal cell carcinoma**, in the following situations:
  - In combination with Inlyta® (axitinib tablets) or Lenvima, for the first-line treatment of advanced disease in adults.
  - For adjuvant treatment of disease that is intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

- **Tumor mutational burden-high (TMB-H) cancer**, for treatment of unresectable or metastatic TMB-H (≥ 10 mutations/megabase) disease, as determined by an FDA-approved test, in adults and pediatric patients that have progressed following prior treatment and who have no satisfactory alternative treatment options.*
  Limitation of Use: The safety and effectiveness of Keytruda in pediatric patients with TMB-H central nervous system cancers have not been established.
- **Urothelial carcinoma**, in the following situations:
  - Treatment of locally advanced or metastatic disease in patients who are not eligible for platinum-containing chemotherapy.
  - Treatment of locally advanced or metastatic urothelial carcinoma in patients who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
  - Treatment of Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer with carcinoma in situ with or without papillary tumors in patients who are ineligible for or have elected not to undergo cystectomy.
  - In combination with Padcev® (enfortumab intravenous infusion), for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy.*

* This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Keytruda. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Keytruda as well as the monitoring required for adverse events and long-term efficacy, approval requires the medication to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Keytruda is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Breast Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E, and F):
   A) Patient is ≥ 18 years of age; AND
   B) Disease is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND
   Note: If the tumor is MSI-H or dMMR, see Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors criteria.
   C) Disease is not tumor mutational burden-high (≥ 10 mutations/megabase); AND
   Note: If the tumor is mutational burden-high, see Tumor Mutational Burden-High (TMB-H) Cancer criteria.
   D) Patient has triple-negative breast cancer (i.e., estrogen receptor-negative, progesterone receptor-negative, human epidermal growth factor receptor 2 [HER2]-negative); AND
   E) Patient meets ONE of the following (i or ii):

i. Patient meets ALL of the following (a, b, and c):
a) Patient has recurrent unresectable (local or regional) or metastatic disease; AND
b) The medication is used in combination with chemotherapy; AND
c) Patient's tumor expression for programmed death-ligand 1 (PD-L1) as determined by an approved test has a combined positive score (CPS) ≥ 10; OR
ii. Patient has high-risk, early-stage disease; AND

F) The medication is prescribed by or in consultation with an oncologist.

2. Cervical Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E, and F):
A) Patient is ≥ 18 years of age; AND
B) Disease is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND
Note: If the tumor is MSI-H or dMMR, see Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors criteria.
C) Disease is not tumor mutational burden-high (≥ 10 mutations/megabase); AND
Note: If the tumor is mutational burden-high, see Tumor Mutational Burden-High (TMB-H) Cancer criteria.
D) Patient has persistent, recurrent, or metastatic disease; AND
E) Patient's tumor expression for programmed death-ligand 1 (PD-L1), as determined by an approved test, has a combined positive score (CPS) ≥ 1; AND
F) The medication is prescribed by or in consultation with an oncologist.

3. Classic Hodgkin Lymphoma. Approve for 1 year if the patient meets BOTH of the following (A and B):
A) Patient meets ONE of the following (i or ii):
i. Patient meets BOTH of the following (a and b):
a) Patient is ≥ 18 years of age; AND
b) Patient has tried at least one systemic regimen; OR
Note: Examples of systemic regimens are ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) + rituximab, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab, CVbP (cyclophosphamide, vinblastine, prednisolone) + rituximab, Adcetris (brentuximab vedotin intravenous infusion) + AVD (doxorubicin, vinblastine, dacarbazine).
ii. Patient meets BOTH of the following (a and b):
a) Patient is < 18 years of age; AND
b) Patient has relapsed or refractory disease; AND

B) The medication is prescribed by or in consultation with an oncologist.

4. Cutaneous Squamous Cell Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has locally advanced, recurrent, or metastatic disease; AND
C) The disease is not curable by surgery or radiation; AND
D) The medication is prescribed by or in consultation with an oncologist.

5. Endometrial Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E, F, and G):
A) Patient is ≥ 18 years of age; AND
B) Disease is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND

Note: If the tumor is MSI-H or dMMR, see Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors criteria.

C) Disease is not tumor mutational burden-high (≥ 10 mutations/megabase); AND
Note: If the tumor is mutational burden-high, see Tumor Mutational Burden-High (TMB-H) Cancer criteria.

D) The medication is used in combination with Lenvima (lenvatinib capsules); AND

E) Patient has progressed on at least one prior systemic therapy; AND
Note: Examples of systemic therapy are carboplatin, paclitaxel, docetaxel, cisplatin, doxorubicin, ifosfamide, everolimus, letrozole.

F) Patient is not a candidate for curative surgery or radiation; AND

G) The medication is prescribed by or in consultation with an oncologist.

6. Esophageal and Esophagogastric Junction Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E, and F):

A) Patient is ≥ 18 years of age; AND

B) Disease is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND
Note: If the tumor is MSI-H or dMMR, see Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors criteria.

C) Disease is not tumor mutational burden-high (≥ 10 mutations/megabase); AND
Note: If the tumor is mutational burden-high, see Tumor Mutational Burden-High (TMB-H) Cancer criteria.

D) Patient meets ONE of the following (i or ii):
- **i.** According to the prescriber, the patient is not a surgical candidate; OR
- **ii.** Patient has unresectable, recurrent, or metastatic disease; AND

E) Patient meets ONE of the following (i, ii, or iii):
- **i.** Patient meets ALL of the following (a, b, and c):
  - **a)** Patient's tumor expression for programmed death-ligand 1 (PD-L1) as determined by an approved test has a combined positive score (CPS) ≥ 10; AND
  - **b)** The medication is used first-line; AND
  - **c)** The medication is used in combination with chemotherapy; OR
    Note: Examples of chemotherapy include cisplatin plus fluorouracil or capecitabine; and oxaliplatin plus fluorouracil or capecitabine.
- **ii.** Patient meets ALL of the following (a, b, and c):
  - **a)** Patient has squamous cell carcinoma; AND
  - **b)** Patient's tumor expression for programmed death-ligand 1 (PD-L1) as determined by an approved test has a combined positive score (CPS) ≥ 10; AND
  - **c)** Patient has tried at least one previous chemotherapy regimen; OR
    Note: Examples of chemotherapy regimens are fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin, fluoropyrimidine and cisplatin, paclitaxel with cisplatin or carboplatin, docetaxel with cisplatin.
- **iii.** Patient meets BOTH of the following (a and b):
  - **a)** Tumor is human epidermal growth factor receptor 2 (HER2) or HER2/neu positive; AND
  - **b)** Medication is used in combination with trastuzumab, cisplatin or oxaliplatin, and fluorouracil or capecitabine; AND

F) The medication is prescribed by or in consultation with an oncologist.

7. Gastric Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):

A) Patient is ≥ 18 years of age; AND

B) Disease is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND

Note: If the tumor is MSI-H or dMMR, see Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors criteria.

C) Disease is not tumor mutational burden-high (≥ 10 mutations/megabase); AND
Note: If the tumor is mutational burden-high, see Tumor Mutational Burden-High (TMB-H) Cancer criteria.

D) Patient meets ALL of the following (i, ii, and iii):
- **i.** Patient has locally advanced unresectable or metastatic disease; AND
- **ii.** Tumor is human epidermal growth factor receptor 2 (HER2) or HER2/neu positive; AND
- **iii.** Medication is used in combination with trastuzumab, cisplatin or oxaliplatin, and fluorouracil or capecitabine; AND

E) The medication is prescribed by or in consultation with an oncologist.

8. Head and Neck Squamous Cell Carcinoma. Approve for 1 year if the patients meets ALL of the following (A, B, C, D, E, and F):

A) Patient is ≥ 18 years of age; AND

B) Disease is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND
Note: If the tumor is MSI-H or dMMR, see Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors criteria.

C) Disease is not tumor mutational burden-high (≥ 10 mutations/megabase); AND
Note: If the tumor is mutational burden-high, see Tumor Mutational Burden-High (TMB-H) Cancer criteria.

D) Patient has recurrent, unresectable, or metastatic disease; AND

E) Patient meets ONE of the following (i or ii):
- **i.** If the medication is used for first-line treatment, patient must meet ONE of the following (a or b):
  - **a)** Keytruda is used in combination with chemotherapy; OR
    Note: Examples of chemotherapy are cisplatin, carboplatin, fluorouracil, gemcitabine.
  - **b)** Keytruda is used as a single agent if the tumors are PD-L1-positive (combined positive score ≥ 1), as determined by an approved test.
- **ii.** For subsequent therapy, patient has tried at least one platinum-containing chemotherapy regimen; AND
  Note: Examples of platinum-contain chemotherapy regimens are: cisplatin or carboplatin with Erbitux (cetuximab intravenous infusion), gemcitabine, or 5-fluorouracil (5-FU).

F) The medication is prescribed by or in consultation with an oncologist.

9. Hepatocellular Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):

A) Patient is ≥ 18 years of age; AND

B) Disease is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND
Note: If the tumor is MSI-H or dMMR, see Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors criteria.

C) Disease is not tumor mutational burden-high (≥ 10 mutations/megabase); AND
Note: If the tumor is mutational burden-high, see Tumor Mutational Burden-High (TMB-H) Cancer criteria.

D) Patient meets ONE of the following (i, ii, or iii):
- **i.** Patient has unresectable disease and is not a transplant candidate; OR
- **ii.** Patient has liver-confined disease, inoperable by performance status, comorbidity, or with minimal or uncertain extrahepatic disease; OR
- **iii.** Patient has metastatic disease or extensive liver tumor burden; AND

E) The medication is prescribed by or in consultation with an oncologist.

10. Melanoma. Approve for the duration noted below if the patient meets ALL of the following (A, B, and C):
Note: This includes cutaneous melanoma, brain metastases due to melanoma and uveal melanoma.
A) Patient meets ONE of the following (i or ii):
i. Approve for 1 year if the patient meets BOTH of the following (a and b):
a) Patient is ≥ 18 years of age; AND
b) Patient has unresectable, advanced, or metastatic melanoma; OR
ii. Approve for up to 1 year (total) if patient meets BOTH of the following (a and b):
a) Patient is ≥ 12 years of age; AND
b) Keytruda will be used as adjuvant treatment; AND
B) The medication is prescribed by or in consultation with an oncologist.

11. Merkel Cell Carcinoma. Approve for 1 year if the patient meets BOTH of the following (A and B):
A) Patient meets ONE of the following (i, ii, or iii):
i. Patient has recurrent locally advanced disease; OR
ii. Patient has recurrent regional disease; OR
iii. Patient has metastatic disease; AND
B) The medication is prescribed by or in consultation with an oncologist.

12. Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors. Approve for 1 year if the patient meets BOTH of the following (A and B):
Note**:** Examples of solid tumors with MSI-H or dMMR are adrenal gland, biliary tract cancers, breast cancer, cervical cancer, chondrosarcoma, colon or rectal cancer, endometrial carcinoma, esophageal or esophagogastric cancers, Ewing sarcoma, gallbladder carcinoma, gastric cancer, head and neck squamous cell carcinoma, hepatocellular carcinoma, occult primary (cancer of unknown primary), osteosarcoma, ovarian/fallopian tube/primary peritoneal, pancreatic adenocarcinoma, penile cancer, neuroendocrine tumor, prostate cancer, small bowel adenocarcinoma, testicular cancer, vulvar cancer.
A) One of the following conditions applies (i, ii, iii, iv, v, vi, vii, or viii):
i. Patient has advanced or metastatic ampullary cancer; OR
ii. Patient has unresectable or metastatic colon or rectal cancer; OR
iii. Patient has unresectable or metastatic gallbladder cancer (including intra- and extra-hepatic cholangiocarcinoma); OR
iv. Patient has unresectable or metastatic head and neck squamous cell carcinoma; OR
v. Patient has persistent or recurrent ovarian/fallopian tube/primary peritoneal carcinoma; OR
vi. Patient has locally advanced or metastatic pancreatic adenocarcinoma; OR
vii. Patient has advanced or metastatic small bowel carcinoma; OR
viii. Patient meets BOTH of the following (a and b):
a) Patient has tried at least one prior systemic therapy for an MSI-H or dMMR solid tumor; AND
b) Patient has unresectable or metastatic disease; AND
B) The medication is prescribed by or in consultation with an oncologist.

13. Non-Small Cell Lung Cancer. Approve for the duration noted if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient meets ONE of the following (i, ii, or iii):
i. Approve for 1 year if the patient meets ALL of the following (a, b, and c):
a) Patient has recurrent, advanced, or metastatic disease; AND
b) Keytruda is used as first-line or continuation maintenance therapy; AND

Note: This is regardless of programmed death-ligand 1 (PD-L1) status.

c) The tumor is negative for actionable mutations; OR
Note: Examples of actionable mutations include sensitizing epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *NTRK* gene fusion-positive, *ROS1, BRAF V600E, MET 14* skipping mutation, *RET* rearrangement.

ii. Approve for 1 year if the patient meets ALL of the following (a, b, and c):

a) Patient has advanced or metastatic disease; AND

b) Keytruda is used as first-line therapy; AND
Note: This is regardless of the PD-L1 status.

c) The tumor is positive for one of the following mutations [(1), (2), or (3)]:

(1) EGFR exon 20 mutation; OR

(2) KRAS G12C mutation; OR

(3) ERBB2 (HER2) mutation; OR

iii. Approve for 1 year if the patient meets ALL of the following (a, b, and c):

a) Patient has recurrent, advanced, or metastatic disease; AND

b) Keytruda is used as first-line or subsequent therapy; AND
Note: This is regardless of the PD-L1 status.

c) The tumor is positive for one of the following mutations [(1), (2), (3), or (4)]:

(1) BRAF V600E mutation; OR

(2) NTRK1/2/3 gene fusion; OR

(3) MET exon 14 skipping mutation; OR

(4) RET rearrangement; OR

iv. Approve for 1 year if the patient meets ALL of the following (a, b, c, and d):

a) Patient has recurrent, advanced, or metastatic disease; AND

b) Keytruda is used as subsequent therapy; AND

c) The tumor is positive for ONE of the following mutations [(1), (2), (3), or (4)]:

(1) EGFR S768I, L861Q, and/or G719X mutation; OR

(2) EGFR exon 19 deletion or exon 21 L858R; OR

(3) ALK rearrangement; OR

(4) ROS1 rearrangement; AND

d) The patient has received targeted drug therapy for the specific mutation; OR
Note: Examples of targeted drug therapy include Gilotrif (afatinib tablet), Tagrisso (osimertinib tablet), erlotinib, Iressa (gefitinib tablet), or Vizimpro (dacomitinib tablet), Xalkori (crizotinib capsule), Rozlytrek (entrectinib capsule), or Zykadia (ceritinib tablet).

v. Approve for 1 year if the patient meets ALL of the following (a, b, c, d, and e):

a) Patient has advanced, recurrent, or metastatic disease; AND

b) Patient has tried systemic therapy; AND
Note: Examples of systemic chemotherapy include cisplatin, carboplatin, pemetrexed, paclitaxel albumin-bound, gemcitabine, paclitaxel.

c) The tumor is PD-L1 positive, with tumor proportion score (TPS) ≥ 1%, as determined by an approved test; AND

d) Patient has not progressed on prior therapy with a programmed death-1 (PD-1)/PD-L1 inhibitor; AND
Note: This includes previous therapy with either one of Keytruda, Opdivo (nivolumab intravenous infusion), or Tecentriq (atezolizumab intravenous infusion).

e) If tumor is positive for an actionable mutation, the patient has received targeted drug therapy for the specific mutation; AND
Note: Examples of actionable mutations include sensitizing epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *NTRK* gene fusion positive, *ROS1, BRAF V600E, MET* exon 14 skipping mutation, *RET* rearrangement.

vi. Approve for 1 year (total) if the patient meets ALL of the following (a, b, and c):
- **a)** Patient has completely resected stage II or III disease; AND
- **b)** Tumor is negative for *EGFR* exon 19 deletion, exon 21 *L858R* mutation, and *ALK* rearrangements; AND
- **c)** Patient has received adjuvant chemotherapy; AND

D) The medication is prescribed by or in consultation with an oncologist.

14. Primary Mediastinal Large B-Cell Lymphoma. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient has relapsed after, or is refractory to, at least two previous regimens; AND
Note: Examples of previous regimens include autologous hematopoietic stem cell transplant (auto-HSCT), EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab), RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone], RCEPP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone).

B) The medication is prescribed by or in consultation with an oncologist.

15. Renal Cell Carcinoma. Approve for the duration noted below if the patient meets ALL of the following (A, B, and C):

A) Patient is ≥ 18 years of age; AND

B) Patient meets ONE of the following (i, ii, or iii):

i. Approve for 1 year if the patient meets ALL of the following (a, b, and c):
- **a)** The tumor has clear cell histology; AND
- **b)** Patient has relapsed or metastatic disease; AND
- **c)** The medication is used in combination with Inlyta (axitinib tablets) or Lenvima (lenvatinib capsules); OR

ii. Approve for 1 year if the patient meets ALL of the following (a, b, and c):
- **a)** The tumor has non-clear cell histology; AND
- **b)** Patient has relapsed or metastatic disease; AND
- **c)** The medication is used as single-agent therapy; OR

iii. Approve for up to 1 year (total) if patient meets ALL of the following (a, b, c, and d):
- **a)** Keytruda is used as adjuvant therapy; AND
- **b)** The tumor has clear cell histology; AND
- **c)** Patient has advanced disease; AND
- **d)** The medication is used as single-agent therapy; AND

C) The medication is prescribed by or in consultation with an oncologist.

16. Tumor Mutational Burden-High (TMB-H) Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient has unresectable or metastatic tumor mutational burden-high (≥ 10 mutations/megabase) solid tumor; AND
Note: Examples of solid tumors are adrenal cancer, ampullary adenocarcinoma, breast cancer, cervical cancer, cholangiocarcinoma (intrahepatic and extrahepatic), chondrosarcoma, chordoma, endometrial carcinoma, esophageal carcinoma, esophagogastric junction carcinoma, Ewing sarcoma, gallbladder cancer, gastric cancer, head and neck cancer, neuroendocrine cancer, osteosarcoma, ovarian/fallopian tube/primary peritoneal carcinoma, pancreatic adenocarcinoma, penile cancer, primary occult, prostate cancer, salivary gland tumors, testicular cancer, thyroid cancer, uterine sarcoma, vulvar cancer.

B) Patient has progressed on prior therapy; AND

C) Patient has no satisfactory alternative treatment options; AND

D) The medication is prescribed by or in consultation with an oncologist.

17. **Urothelial Carcinoma.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
    A) Patient is ≥ 18 years of age; AND
    B) Patient meets ONE of the following conditions (i, ii, or iii):
    i. Patient has tried at least one platinum-based chemotherapy; OR
    Note: Cisplatin and carboplatin are platinum-based chemotherapies.
    ii. According to the prescriber, patient is not eligible for platinum-based chemotherapy (i.e., with cisplatin and carboplatin); OR
    Note: This is regardless of PD-L1 status.
    iii. Patient meets both of the following (a and b):
    a) Patient has non-muscle invasive bladder cancer; AND
    b) Patient has tried Bacillus Calmette-Guerin (BCG) or intravesical chemotherapy; AND
    Note: Examples of agents used as intravesical chemotherapy include mitomycin and gemcitabine.
    C) The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

18. **Adrenal Gland Tumor.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
    A) Patient is ≥ 18 years of age; AND
    B) Patient has unresectable or metastatic adrenocortical carcinoma; AND
    C) The medication is prescribed by or in consultation with an oncologist.

19. **Anal Carcinoma.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
    A) Patient is ≥ 18 years of age; AND
    B) Patient has received at least one other chemotherapy regimen; AND
    Note: Examples of chemotherapy regimens are 5-fluorouracil (5-FU), cisplatin, carboplatin, paclitaxel, FOLFOX (oxaliplatin, leucovorin, and 5-FU).
    C) The medication is prescribed by or in consultation with an oncologist.

20. **Extranodal NK/T-Cell Lymphoma, Nasal Type.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
    A) Patient is ≥ 18 years of age; AND
    B) Patient has received an asparaginase-based chemotherapy regimen; AND
    Note: Examples of asparaginase-based chemotherapy are dexamethasone, ifosfamide, pegaspargase, etoposide; and gemcitabine, pegaspargase, oxaliplatin.
    C) The medication is prescribed by or in consultation with an oncologist.

21. **Gestational Trophoblastic Neoplasia.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
    A) Patient is ≥ 18 years of age; AND
    B) Patient meets ONE of the following (i or ii):
    i. Patient has tried at least one previous chemotherapy regimen for recurrent or progressive disease; OR
    Note: Examples of chemotherapy regimens contain etoposide, cisplatin/carboplatin, paclitaxel, bleomycin, ifosfamide, methotrexate.
    ii. Patient has high-risk disease; AND
    C) The medication is prescribed by or in consultation with an oncologist.

22. Glioma. Approve for duration noted if the patient meets ALL of the following (A, B, C, D, and E):

A) Patient is < 18 years of age; AND

B) Patient has diffuse high-grade disease; AND

C) Tumor is hypermutant; AND

D) Patient meets ONE of the following (i or ii):

i. Approve for 1 year (total) if the patient meets BOTH of the following (a and b):

a) Medication is used for adjuvant treatment; AND

b) Patient does NOT have diffuse midline glioma, H3 K27-altered or pontine location; OR

ii. Approve for 1 year of the patient has meets BOTH of the following (a and b):

a) Patient has recurrent or progressive; AND

b) Patient does NOT have either of the following [(1) or (2)]:

(1) Oligodendroglioma isocitrate dehydrogenase (IDH)-mutant and 1p/19q co-deleted; OR

(2) Astrocytoma, IDH-mutant; AND

E) The medication is prescribed by or in consultation with an oncologist.

23. Kaposi Sarcoma. Approve for duration noted if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient has endemic or classic Kaposi sarcoma; AND

C) Patient has relapsed or refractory advanced cutaneous, oral, visceral, or nodal disease; AND

D) The medication is prescribed by or in consultation with an oncologist.

24. Mycosis Fungoides/Sezary Syndrome. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient is ≥ 18 years of age; AND

B) The medication is prescribed by or in consultation with an oncologist.

25. Primary Cutaneous Anaplastic Large Cell Lymphoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient has relapsed or refractory disease; AND

C) Patient meets ONE of the following (i or ii):

ii. Patient has disease with multifocal lesions; OR

iii. Patient has disease with regional node; AND

D) The medication is prescribed by or in consultation with an oncologist.

26. Small Cell Lung Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, and C):

A) Patient is ≥ 18 years of age; AND

B) Keytruda is used as subsequent therapy; AND

C) The medication is prescribed by or in consultation with an oncologist.

27. Soft Tissue Sarcoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Disease is not tumor mutational burden-high (≥ 10 mutations/megabase); AND

Note: If the tumor is mutational burden-high, see Tumor Mutational Burden-High (TMB-H) Cancer criteria.

C) Patient has ONE of the following (i, ii, iii, or iv):

i. Alveolar soft part sarcoma; OR

ii. Cutaneous angiosarcoma; OR
iii. Extremity, body wall, or head and neck sarcoma; OR
iv. Retroperitoneal or intra-abdominal sarcoma; AND
D) The medication is prescribed by or in consultation with an oncologist.

28. Squamous Cell Skin Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has locally advanced, recurrent, or metastatic disease; AND
C) According to the prescriber, curative surgery and curative radiation therapy are not feasible; AND
D) The medication is prescribed by or in consultation with an oncologist.

27. Thymic Carcinoma. Approve for 1 year if the patient meets BOTH of the following (A and B):
A) Patient is ≥ 18 years of age; AND
B) The medication is prescribed by or in consultation with an oncologist.

28. Vulvar Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E, and F):
A) Patient is ≥ 18 years of age; AND
B) Disease is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND
Note: If the tumor is MSI-H or dMMR, see Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors criteria.
C) Disease is not tumor mutational burden-high (≥ 10 mutations/megabase); AND
Note: If the tumor is mutational burden-high, see Tumor Mutational Burden-High (TMB-H) Cancer criteria.
D) The tumor is PD-L1-positive (combined positive score ≥ 1), as determined by an approved test; AND
E) Patient has tried at least one other chemotherapy regimen; AND
Note: Examples of chemotherapy regimen are cisplatin, carboplatin, fluorouracil, paclitaxel.
F) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Keytruda is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable – Programmed Death Receptor-1) – Libtayo Prior Authorization Policy
- Libtayo® (cemiplimab-rwlc intravenous infusion – Regeneron/Sanofi Genzyme)

REVIEW DATE: 12/13/2023

OVERVIEW

Libtayo, a programmed death receptor-1 (PD-1) blocking antibody, is indicated for the treatment of the following conditions:[1]

- **Basal Cell Carcinoma**, for treatment of patients with locally advanced or metastatic disease previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate.
- **Cutaneous Squamous Cell Carcinoma**, for metastatic or locally advanced disease in patients who are not candidates for curative surgery or curative radiation.
- **Non-Small Cell Lung Cancer (NSCLC)**, for first-line treatment, as a single agent, in adults with tumors that have high programmed death-ligand 1 (PD-L1) expression (tumor proportion score [TPS] ≥ 50%), as determined by an FDA-approved test, with no epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), or ROS1 aberrations. The disease can be locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or for metastatic disease.
- **NSCLC**, for first-line treatment, in combination with platinum-based chemotherapy, for adults with NSCLC without EGFR, ALK, or ROS1 aberrations and with disease that is locally advanced where patients are not candidates for surgical resection or definitive chemoradiation, or for metastatic disease.

GUIDELINES

Libtayo is addressed in National Comprehensive Cancer Network guidelines:

- **Basal Cell Carcinoma:** Guidelines (version 2.2024 – September 14, 2023) recommend Libtayo for locally advanced disease where surgery and/or radiation therapy may not result in a cure or would possibly produce a significant functional limitation, for nodal disease if surgery is not feasible, or metastatic disease (category 2A).[2,5]
- **Cervical Cancer:** Guidelines (version 1.2024 – September 20, 2023) recommend Libtayo for the subsequent treatment of local or regional recurrence, or stage IVB or recurrence with distant metastases, as a single agent (category 2A).[5,6]
- **Cutaneous Squamous Cell Carcinoma:** Guidelines (version 1.2024 – November 9, 2023) recommend Libtayo as a preferred therapy (category 2A) for locally advanced, recurrent, or metastatic disease in which curative surgery or curative radiotherapy are not feasible.[3,5] Libtayo is also recommended for the adjuvant treatment of very-high risk, locally advanced, unresectable, or regional disease.
- **Non-Small Cell Lung Cancer:** Guidelines (version 5.2023 – November 8, 2023) recommend Libtayo as a single agent for the first-line and continuation maintenance therapy of advanced, recurrent, or metastatic disease with PD-L1 ≥ 50% and negative for actionable molecular markers.[4,5] Libtayo is also recommended as a single agent or in combination with chemotherapy, as first-line, continuation maintenance, and subsequent therapy in a variety of clinical situations.
- **Vulvar Cancer:** Guidelines (version 2.2024 – October 26, 2023) recommend single agent Libtayo for the subsequent treatment of advanced, recurrent, or metastatic disease.[5,7]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Libtayo. Because of the specialized skills required for evaluation and diagnosis of patients treated with Libtayo as well as the monitoring required for adverse events and long-term efficacy, approval requires Libtayo to be prescribed by, or in consultation with, a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Libtayo is recommended in those who meet one of the following criteria:

FDA-Approved Indications

67. Basal Cell Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has locally advanced, nodal, or metastatic disease; AND
- **C)** The medication is prescribed by or in consultation with an oncologist.

68. Cutaneous Squamous Cell Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following (i or ii):
  - **i.** Patient meets BOTH of the following (a and b):
    - **a)** Patient has locally advanced, recurrent, or metastatic disease; AND
    - **b)** Patient is not a candidate for curative surgery or curative radiation; OR
  - **ii.** Patient meets BOTH of the following (a and b):
    - **a)** Patient has very-high risk, locally advanced, unresectable, or regional disease; AND
    - **b)** Medication will be used as neoadjuvant therapy; AND
- **C)** The medication is prescribed by or in consultation with an oncologist.

3. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has recurrent, advanced, or metastatic disease; AND
- **C)** Patient meets ONE of the following (i, ii, iii, or iv):
  - **i.** Patient meets BOTH of the following (a and b):
    - **a)** Medication is used for first-line or continuation maintenance therapy; AND
      D) Note: This is regardless of programmed death-ligand 1 (PD-L1) status.
    - **b)** The tumor is negative for actionable mutations; OR
      Note: Examples include sensitizing epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *RET* rearrangement, *MET* exon 14 skipping, *NTRK* gene fusion positive, *BRAF V600E* mutation-positive, and *ROS1* rearrangement positive.
  - **ii.** Patient meets BOTH of the following (a and b):
    - **a)** Medication will be used first-line; AND
    - **b)** The tumor is positive for ONE of the following mutations [(1), (2), or (3)]:

(4) EGFR exon 20 mutation; OR
(5) KRAS G12C mutation; OR
(6) ERBB2 (HER2) mutation; OR

iii. Patient meets BOTH of the following (a and b):

a) Medication will be used as first-line or subsequent therapy; AND
E) Note: This is regardless of the PD-L1 status.
b) The tumor is positive for ONE of the following mutations [(1), (2), (3), or (4)]:
(1) BRAF V600E mutation; OR
(2) NTRK1/2/3 gene fusion; OR
(3) MET exon 14 skipping mutation; OR
(4) RET rearrangement; OR

iv. Patient meets ALL of the following (a, b, and c):

a) Medication will be used as subsequent therapy; AND
b) The tumor is positive for ONE of the following mutations [(1), (2), (3), or (4)]:
(1) EGFR S768I, L861Q, and/or G719X mutation; OR
(2) EGFR exon 19 deletion or exon 21 L858R; OR
(3) ALK rearrangement; OR
(4) ROS1 rearrangement; AND
c) The patient has received targeted drug therapy for the specific mutation; OR
F) Note: Examples of targeted drug therapy include Gilotrif (afatinib tablet), Tagrisso (osimertinib tablet), erlotinib, Iressa (gefitinib tablet), Vizimpro (dacomitinib tablet) Xalkori (crizotinib capsule), Rozlytrek (entrectinib capsule), Alecensa (alectinib capsule), or Zykadia (ceritinib tablet).

G) The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

4. Cervical Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient meets ONE of the following (i or ii):
i. Patient has local or regional recurrence; OR
ii. Patient has distant metastatic disease; AND
C) Medication is used as subsequent therapy; AND
D) The medication is prescribed by or in consultation with an oncologist.

5. Vulvar Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has advanced, recurrent, or metastatic disease; AND
C) Medication is used as subsequent therapy; AND
D) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Libtayo is not recommended in the following situations:

134. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable – Programmed Death Receptor-1) - Loqtorzi Prior Authorization Policy
- Loqtorzi™ (toripalimab intravenous infusion – Coherus BioSciences)

REVIEW DATE: 12/20/2023

OVERVIEW

Loqtorzi, a programmed death receptor-1 blocking antibody, is indicated for the following uses:[1]
- **Nasopharyngeal carcinoma**, in adults for the first-line treatment of metastatic or recurrent, locally advanced disease in combination with cisplatin and gemcitabine.
- **Nasopharyngeal carcinoma**, in adults as a single agent for the treatment of previously treated unresectable or metastatic disease.

Guidelines

The National Comprehensive Cancer Network (NCCN) head and neck cancers (version 2.2024 – December 8, 2023) clinical practice guidelines recommend Loqtorzi in combination with cisplatin and gemcitabine as a "Preferred Regimen" for the first-line treatment of recurrent, unresectable, oligometastatic, or metastatic nasopharyngeal carcinoma without any surgical or radiation therapy options (category 1).[2,3] Loqtorzi is recommended as a single agent, as a "Preferred Regimen" for the subsequent treatment of nasopharyngeal carcinoma if disease progression on or after platinum-containing therapy (category 2A). It is also an "Other Recommended Regimen" for the subsequent treatment of nasopharyngeal carcinoma, in combination with cisplatin and gemcitabine if not previously used (category 2A).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Loqtorzi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Loqtorzi as well as the monitoring required for adverse events and long-term efficacy, approval requires Loqtorzi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Loqtorzi is recommended in those who meet the following criteria:

FDA-Approved Indication

177. Nasopharyngeal Carcinoma. Approve for 1 year if the patient meets the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has recurrent, unresectable, oligometastatic, or metastatic disease; AND
- **C)** Patient meets ONE of the following (i or ii):
  - **i.** Patient meets BOTH of the following (a and b):
    - **a)** Loqtorzi is used for first-line treatment; AND

b) Loqtorzi is used in combination with cisplatin and gemcitabine; OR

ii. Patient meets both of the following (a and b):

a) Loqtorzi is used for subsequent treatment; AND

b) Loqtorzi is used as a single agent; AND

D) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Loqtorzi is not recommended in the following situations:

273. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable – Programmed Death Receptor-1) – Opdivo Prior Authorization Policy
- Opdivo® (nivolumab intravenous infusion – Bristol-Myers Squibb)

REVIEW DATE: 02/08/2023; selected revision 08/23/2023

OVERVIEW

Opdivo, a human programmed death receptor-1 (PD-1) blocking antibody, is indicated for the following uses:[1]

- **Classical Hodgkin lymphoma**, for adults who have relapsed or progressed after autologous hematopoietic stem cell transplantation (auto-HSCT) and Adcetris® (brentuximab vedotin intravenous infusion) OR three or more lines of systemic therapy that includes auto-HSCT.*
- **Colorectal cancer**, with or without Yervoy® (ipilimumab intravenous infusion) for patients ≥ 12 years of age with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic disease that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.*
- **Esophageal carcinoma**, in the following situations:
  - For patients with unresectable advanced, recurrent, or metastatic squamous cell disease after prior fluoropyrimidine- and platinum-based chemotherapy.
  - Adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in patients who have received neoadjuvant chemoradiotherapy.
  - First-line treatment of adults with unresectable advanced or metastatic esophageal squamous cell carcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy.
  - First-line treatment of adults with unresectable advanced or metastatic esophageal squamous cell carcinoma in combination with Yervoy.
- **Gastric cancer, esophagogastric junction cancer, and esophageal adenocarcinoma**, for patients with advanced or metastatic disease, in combination with fluoropyrimidine- and platinum-containing chemotherapy.
- **Head and neck squamous cell carcinoma**, in patients with recurrent or metastatic disease with disease progression on or after platinum-based therapy.
- **Hepatocellular carcinoma**, in patients who have been previously treated with Nexavar® (sorafenib tablets), in combination with Yervoy.*
- **Malignant pleural mesothelioma**, for first-line treatment, in combination with Yervoy in adults with unresectable disease.
- **Melanoma**, in patients with:
  - Unresectable or metastatic disease as a single agent.
  - Unresectable or metastatic disease in combination with Yervoy.
  - Adjuvant treatment for lymph node involvement or metastatic disease in patients who have undergone complete resection.
- **Non-small cell lung cancer**:
  - As first-line treatment in combination with Yervoy, in adults with metastatic disease expressing programmed death-ligand 1 (≥ 1%) as determined by an FDA-approved test, without epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations.

- As first-line treatment in combination with Yervoy and two cycles of platinum-doublet chemotherapy, in adults with recurrent or metastatic disease without *EGFR* or *ALK* genomic tumor aberrations.
- In patients with metastatic disease and progression on or after platinum-based chemotherapy. Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Opdivo.
- In combination with platinum-doublet chemotherapy, as neoadjuvant treatment of adults with resectable (tumors ≥ 4 cm or node positive) disease.

- **Renal cell carcinoma**:
  - In patients with advanced disease who have received prior anti-angiogenic therapy.
  - In combination with Yervoy, for patients with intermediate or poor risk and previously untreated advanced disease.
  - In combination with Cabometyx® (cabozantinib tablets), for the first-line treatment of patients with advanced disease.
- **Urothelial carcinoma**, in the following situations:
  - In patients with advanced or metastatic disease who have disease progression during or following platinum-containing chemotherapy.
  - In patients with advanced or metastatic disease who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
  - Adjuvant treatment of patients at high risk of recurrence after undergoing radical resection of urothelial carcinoma.

* This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

POLICY STATEMENT

i. Prior Authorization is recommended for prescription benefit coverage of Opdivo. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Opdivo as well as the monitoring required for adverse events and long-term efficacy, approval requires the medication to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Opdivo is recommended in those who meet one of the following criteria:

FDA-Approved Indications

7. Classic Hodgkin Lymphoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **G)** Note: For pediatric patients, see Pediatric Hodgkin Lymphoma criteria.
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets one of the following conditions (i, ii, iii, or iv):
  - **i.** Patient has had a hematopoietic stem cell transplantation (HSCT); OR
  - **ii.** Patient has tried three or more systemic regimens AND this includes an auto-HSCT as one line of therapy; OR

H) Note: Examples are ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), Sanford V (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone), escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone).

i. Patient has relapsed or refractory disease and the medication is used in combination with Adcetris (brentuximab intravenous infusion) or ICE (ifosfamide, carboplatin, and etoposide); OR

ii. Patient is not eligible for transplant according to the prescriber; AND

C) The medication is prescribed by or in consultation with an oncologist.

8. Colon, Rectal, or Appendiceal Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 12 years of age; AND

B) The tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND

C) Patient meets one of the following (i, ii, or iii):

i. Patient has tried chemotherapy; OR

I) Note: Examples of chemotherapy are fluoropyrimidine such as 5-fluorouracil (5-FU), capecitabine, oxaliplatin, irinotecan, or an adjunctive chemotherapy regimen such as FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).

ii. Patient has unresectable, advanced, or metastatic disease; OR

iii. The medication is used for neoadjuvant therapy; AND

D) The medication is prescribed by or in consultation with an oncologist.

9. Esophageal and Esophagogastric Junction Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):

A) Patient is ≥ 18 years of age; AND

B) Patient meets ONE of the following (i, ii, iii, or iv):

i. Patient meets BOTH of the following (a and b):

a) Patient has received preoperative chemotherapy; AND

J) Note: Examples of chemotherapy include 5-fluorouracil plus either cisplatin or oxaliplatin; and paclitaxel plus carboplatin.

b) According to the prescriber, the patient has residual disease; OR

ii. Patient meets ALL of the following (a, b, and c):

a) Patient has squamous cell carcinoma; AND

b) Patient meets ONE of the following criteria [(1) or (2)]:

(1) According to the prescriber, the patient is not a surgical candidate; OR

(2) Patient has unresectable locally advanced, recurrent, or metastatic disease; AND

c) Patient has tried chemotherapy; OR

K) Note: Examples of chemotherapy include fluoropyrimidines (5-fluorouracil [5-FU] and capecitabine) plus either cisplatin or oxaliplatin, paclitaxel plus carboplatin, or cisplatin plus either docetaxel or paclitaxel.

iii. Patient meets ALL of the following (a, b, c, d, and e):

a) Patient has adenocarcinoma; AND

b) Patient meets ONE of the following criteria [(1) or (2)]:

(1) According to the prescriber, the patient is not a surgical candidate; OR

(2) Patient has unresectable locally advanced, recurrent, or metastatic disease; AND

c) The disease is negative for human epidermal growth factor receptor 2 (HER2) overexpression; AND

d) The tumor expression for programmed death ligand-1 (PD-L1) has a combined positive score (CPS) ≥ 5; AND

e) The medication is used in combination with fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin; OR

iv. Patient meets ALL of the following (a, b, c, d, and e):

a) Patient has squamous cell carcinoma; AND

b) Patient meets ONE of the following [(1) or (2)]:

(1) According to the prescriber, the patient is not a surgical candidate; OR

(2) Patient has unresectable locally advanced, recurrent, or metastatic disease; AND

c) The disease is negative for human epidermal growth factor receptor 2 (HER2) overexpression; AND

d) The medication will be used for first-line therapy; AND

e) The medication will be used in combination with ONE of the following [(1) or (2)]:

(1) Fluoropyrimidine and platinum containing chemotherapy; OR

L) Note: Examples of fluoropyrimidines include 5-fluorouracil and capecitabine and examples of platinum agents include cisplatin and carboplatin.

(2) Yervoy (ipilimumab intravenous infusion); AND

C) The medication is prescribed by or in consultation with an oncologist.

10. Gastric Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E, and F):

A) Patient is ≥ 18 years of age; AND

B) Patient meets ONE of the following (i or ii):

i. Patient has unresectable locally advanced, recurrent, or metastatic disease; OR

ii. According to the prescriber, the patient is not a surgical candidate; AND

C) The disease is negative for human epidermal growth factor receptor 2 (HER2) overexpression; AND

D) The tumor expression for programmed death ligand-1 (PD-L1) has a combined positive score (CPS) ≥ 5; AND

E) The medication is used in combination with fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin; AND

F) The medication is prescribed by or in consultation with an oncologist.

M)

11. Head and Neck Squamous Cell Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):

A) Patient is ≥ 18 years of age; AND

B) Patient meets ONE of the following (i or ii):

i. Patient has non-nasopharyngeal disease; OR

ii. Patient meets ALL of the following conditions (a, b, and c):

a) Patient has nasopharyngeal disease; AND

b) Patient has recurrent, unresectable, oligometastatic, or metastatic disease; AND

c) Opdivo is used in combination with cisplatin and gemcitabine; AND

C) The medication is prescribed by or in consultation with an oncologist.

12. Hepatocellular Carcinoma, Including Hepatobiliary Cancers. Approve for 1 year if the patient meets ALL of the following (A, B, and C):

F) Patient is ≥ 18 years of age; AND

G) Patient has tried at least one tyrosine kinase inhibitor; AND
Note: Examples are Nexavar (sorafenib tablets), Lenvima (lenvatinib capsules).

H) The medication is prescribed by or in consultation with an oncologist.

N)

13. Melanoma. Approve for the duration noted if the patient meets ALL of the following (A, B, and C):
Note: This includes cutaneous melanoma, brain metastases due to melanoma, and uveal melanoma.

A) Patient is ≥ 18 years of age; AND
B) Patient meets ONE of the following (i or ii):
  i. Approve for 1 year if the patient has unresectable, advanced, or metastatic melanoma; OR
  ii. Approve for up to 1 year of treatment (total) if Opdivo will be used as adjuvant treatment; AND
  Note: Examples are in a patient with no evidence of disease following resection of node-positive disease, locoregional recurrence, or in-transit recurrence.
C) The medication is prescribed by or in consultation with an oncologist.

14. Mesothelioma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has ONE of the following (i, ii, iii, or iv):
  i. Malignant pleural mesothelioma; OR
  ii. Malignant peritoneal mesothelioma; OR
  iii. Pericardial mesothelioma; OR
  iv. Tunica vaginalis testis mesothelioma; AND
C) If used as first-line therapy, the patient meets the following (i and ii):
  i. The patient has unresectable disease; AND
  ii. The medication is used in combination with Yervoy (ipilimumab intravenous infusion); AND
D) The medication is prescribed by or in consultation with an oncologist.
O)

15. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patient meets one of the following (i, ii, iii, iv, v, or vi):
  i. Opdivo is used as first-line or continuation maintenance therapy and the patient meets ALL of the following (a, b, and c):
  P) Note: This is regardless of programmed death-ligand-1 (PD-L1) status.
    a) Patient has recurrent, advanced, or metastatic disease; AND
    b) Opdivo will be used in combination with Yervoy (ipilimumab intravenous infusion); AND
    c) The tumor is negative for actionable mutations; OR
    Q) Note: Examples of actionable mutations include sensitizing epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *NTRK* gene fusion-positive, *ROS1, BRAF V600E, MET 14* skipping mutation, *RET* rearrangement.
  ii. Opdivo is used as first-line therapy and the patient meets ALL of the following (a, b, and c):
  R) Note: This is regardless of PD-L1 status.
  a) Patient has recurrent, advanced, or metastatic disease; AND
  b) The tumor is positive for one of the following mutations [(1), (2), (3), or (4)]:
    (1) *BRAF V600E* mutation; OR
    (2) *NTRK1/2/3* gene fusion; OR
    (3) *MET* exon 14 skipping mutation; OR
    (4) *RET* rearrangement; AND
  c) The medication will be used in combination with Yervoy (ipilimumab intravenous infusion); OR
  iii. Opdivo is used as first-line or subsequent therapy and the patient meets ALL of the following (a, b, and c):
  S) Note: This is regardless of PD-L1 status.
    a) Patient has recurrent, advanced, or metastatic disease; AND
    b) The tumor is positive for one of the following mutations [(1), (2), or (3)]:
  (1) Epidermal growth factor receptor (*EGFR*) exon 20 mutation; OR

(2) *KRAS G12C* mutation; OR
(3) *ERBB2* (*HER2*); AND
c) The medication will be used in combination with Yervoy (ipilimumab intravenous infusion); OR

iv. Opdivo is used as subsequent therapy and the patient meets ALL of the following (a, b, c, and d):
a) Patient has recurrent, advanced, or metastatic disease; AND
b) The tumor is positive for one of the following mutations [(1), (2), (3), or (4)]:
(1) Epidermal growth factor receptor (*EGFR*) *S768I*, *L861Q*, and/or *G719X* mutation positive; OR
(2) *EGFR* exon 19 deletion or exon 21 L858R; OR
(3) Anaplastic lymphoma kinase (*ALK*) rearrangement positive; OR
(4) *ROS1* rearrangement positive; AND
c) The patient has received targeted drug therapy for the specific mutation; AND
T) Note: Examples of targeted drug therapy include Gilotrif (afatinib tablet), Tagrisso (osimertinib tablet), erlotinib, Iressa (gefitinib tablet), Vizimpro (dacomitinib tablet), Xalkori (crizotinib capsule), Rozlytrek (entrectinib capsule), or Zykadia (ceritinib tablet).
d) Opdivo is used in combination with Yervoy (ipilimumab intravenous infusion); OR

v. Patient meets ALL of the following (a, b, c, and d):
a) Patient has recurrent, advanced, or metastatic disease; AND
b) Patient has tried systemic chemotherapy; AND
U) Note: Examples of systemic chemotherapy include cisplatin, carboplatin, Alimta (pemetrexed injection), Abraxane (paclitaxel albumin-bound injection), gemcitabine, paclitaxel.
c) Patient has not progressed on prior therapy with a programmed death-1 (PD-1)/PD-L1 inhibitor; AND
V) Note: This includes previous therapy with either one of Opdivo, Keytruda (pembrolizumab intravenous infusion), or Tecentriq (atezolizumab intravenous infusion).
d) If the tumor is positive for an actionable mutation, the patient has received targeted drug therapy for the specific mutation; AND
W) Note: Examples of actionable mutations include sensitizing epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *NTRK* gene fusion-positive, *ROS1*, *BRAF V600E*, *MET 14* skipping mutation, *RET* rearrangement; OR

vi. Patient meets ALL of the following (a, b, and c):
a) Patient has resectable disease; AND
X) Note: Resectable disease is defined as tumors ≥ 4 cm or node positive.
b) Opdivo is used as neoadjuvant therapy; AND
c) Opdivo is used in combination with platinum-doublet chemotherapy; AND
Y) Note: Examples of platinum-doublet chemotherapy include carboplatin plus paclitaxel, cisplatin plus pemetrexed, and cisplatin plus gemcitabine.

C) The medication is prescribed by or in consultation with an oncologist.
Z)

16. Renal Cell Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patient has advanced, relapsed, or metastatic disease; AND
C) The medication is prescribed by or in consultation with an oncologist.

17. Urothelial Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
A) Patient is ≥ 18 years of age; AND

B) Patient meets ONE of the following (i or ii):
- **i.** Patient has tried at least one other chemotherapy regimen; OR
  AA) Note: Examples of chemotherapy regimens are cisplatin, carboplatin, gemcitabine.
- **ii.** Patient is at high risk of recurrence after radical resection of the tumor; AND

C) The medication is prescribed by or in consultation with an oncologist.

ii. Other Uses with Supportive Evidence

18. Ampullary Adenocarcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
- **D)** Patient is ≥ 18 years of age; AND
- **E)** Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease; AND
- **F)** Patient meets ONE of the following (i or ii):
  a. The medication is used first-line and the patient has ONE of the following (a, b, or c):
     a) Unresectable localized disease; OR
     b) Stage IV resected disease; OR
     c) Metastatic disease at initial presentation; OR
  b. The medication is used for subsequent therapy; AND
- **G)** The medication is used in combination with Yervoy (ipilimumab intravenous infusion); AND
- **H)** The medication is prescribed by or in consultation with an oncologist.

19. Anal Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has tried at least one chemotherapy regimen; AND
  BB) Note: Examples of chemotherapy are 5-fluorouracil (5-FU), cisplatin, carboplatin plus paclitaxel, FOLFOX (oxaliplatin, leucovorin, and 5-FU).
- **C)** The medication is prescribed by or in consultation with an oncologist.

14. Bone Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E, F, G, and H):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has one of the following conditions (i, ii, iii, iv, or v):
  - **i.** Chondrosarcoma; OR
  - **ii.** Chordoma; OR
  - **iii.** Ewing sarcoma; OR
  - **iv.** Osteosarcoma; OR
  - **v.** High-grade undifferentiated pleomorphic sarcoma; AND
- **C)** Patient has unresectable or metastatic disease; AND
- **D)** Patient has tumor mutational burden-high (TMB-H) disease; AND
- **E)** Patient has progressed following prior treatment; AND
- **F)** Patient has no satisfactory alternative treatment options; AND
- **G)** The medication is used in combination with Yervoy (ipilimumab intravenous infusion); AND
- **H)** The medication is prescribed by or in consultation with an oncologist.

CC)

15. Cervical Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient has programmed death ligand-1 (PD-L1) positive disease (combined positive score [CPS] ≥ 1); AND
C) The medication is used as second-line or subsequent therapy; AND
D) The medication is prescribed by or in consultation with an oncologist.

DD)

16. Diffuse High-Grade Gliomas. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is < 18 years of age; AND
B) Patient has hypermutant tumor diffuse high-grade glioma; AND
C) Patient meets ONE of the following (i or ii):
i. The medication is used for adjuvant treatment; OR
ii. The medication is used for recurrent or progressive disease; AND
D) The medication is prescribed by or in consultation with an oncologist.

17. Endometrial Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has tried at least one prior systemic therapy; AND
EE) Note: Examples are carboplatin, paclitaxel, docetaxel, cisplatin, doxorubicin, topotecan, ifosfamide, everolimus/letrozole.
C) Patient has mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) disease; AND
D) The medication is prescribed by or in consultation with an oncologist.

FF)

18. Extranodal NK/T-Cell Lymphomas. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patient has received an asparaginase-based chemotherapy regimen; AND
GG) Note: Examples of asparaginase-based chemotherapy are dexamethasone, ifosfamide, pegaspargase, etoposide; and gemcitabine, pegaspargase, oxaliplatin.
C) The medication is prescribed by or in consultation with an oncologist.

HH)

19. Gestational Trophoblastic Neoplasia. Approve for 1 year if the patient meets BOTH of the following (A and B):
A) Patient meets one of the following (i or ii):
i. Patient has tried at least one previous chemotherapy regimen for recurrent or progressive disease; OR
II) Note: Examples of chemotherapy regimens contain etoposide, cisplatin/carboplatin, paclitaxel, bleomycin, ifosfamide, methotrexate.
ii. Patient has methotrexate-resistant high-risk disease; AND
B) The medication is prescribed by or in consultation with an oncologist.

JJ)

20. Kaposi Sarcoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient has classic disease; AND
B) Patient has relapsed or refractory disease; AND
C) The medication is used in combination with Yervoy (ipilimumab intravenous infusion); AND
D) The medication is prescribed by or in consultation with an oncologist.

21. Merkel Cell Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patient meets ONE of the following (i or ii):

i. Patient has disseminated Merkel cell carcinoma; OR
ii. The medication is used as neoadjuvant therapy; AND

C) The medication is prescribed by or in consultation with an oncologist.

22. Neuroendocrine Tumors. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):

A) Patient is ≥ 18 years of age; AND
B) Patient has advanced or metastatic disease; AND
C) Patient meets one of the following (i or ii):
i. Patient has well differentiated, Grade 3 disease; OR
ii. Patient has poorly differentiated, large or small cell disease (other than lung); AND
D) The medication is used in combination with Yervoy (ipilimumab intravenous infusion); AND
E) The medication is prescribed by or in consultation with an oncologist.

KK)

23. Pediatric Hodgkin Lymphoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient is < 18 years of age; AND
B) Patient has tried at least one prior systemic chemotherapy; AND

LL) Note: Examples are AVPC (doxorubicin, vincristine, prednisone, cyclophosphamide), ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide), OEPA (vincristine, etoposide, prednisone, doxorubicin).

C) If used for re-induction therapy, the medication is used in combination with Adcetris (brentuximab intravenous infusion); AND
D) The medication is prescribed by or in consultation with an oncologist.

MM)

24. Primary Mediastinal Large B-Cell Lymphoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):

A) Patient has relapsed or refractory disease; AND
B) Patient meets ONE of the following (i or ii):
i. The medication is used as a single agent; OR
ii. The medication is used in combination with Adcetris (brentuximab intravenous infusion) after a partial response to therapy for relapsed or refractory disease; AND
C) The medication is prescribed by or in consultation with an oncologist.

25. Small Bowel Adenocarcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND
B) Patient has advanced or metastatic disease; AND
C) The tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND
D) The medication is prescribed by or in consultation with an oncologist.

NN)

26. Small Cell Lung Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, and C):

A) Patient is ≥ 18 years of age; AND
B) The medication is used as second-line or subsequent therapy; AND
C) The medication is prescribed by or in consultation with an oncologist.

OO)

27. Vulvar Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND
B) Patient has human papilloma virus (HPV)-related disease; AND
C) Patient has tried at least one prior systemic therapy; AND

PP) Note: Examples are cisplatin, carboplatin, fluorouracil, paclitaxel, bevacizumab.

D) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Opdivo is not recommended in the following situations:

135. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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QQ)

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable – Programmed Death Receptor-1) – Opdualag Prior Authorization Policy
- Opdualag™ (nivolumab and relatlimab-rmbw intravenous infusion – Bristol-Myers Squibb)

REVIEW DATE: 03/29/2023

OVERVIEW

Opdualag, a combination of a programmed death receptor-1 (PD-1) blocking antibody and a lymphocyte activation gene-3 (LAG-3) blocking antibody, is indicated for the treatment of unresectable or metastatic **melanoma** in patients ≥ 12 years of age.[1]

Guidelines

The National Comprehensive Cancer Network clinical practice guidelines for **cutaneous melanoma** (version 2.2023 – March 10, 2023) recommend Opdualag as a preferred first-line treatment option for patients with metastatic or unresectable disease (category 1).[2,3] Opdualag is also recommended for second-line or subsequent treatment, and for re-induction therapy in patients with disease control with previous anti-PD-1/LAG-3 therapy and disease progression or relapse occurring > 3 months after treatment discontinuation (category 2A).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Opdualag. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Opdualag as well as the monitoring required for adverse events and long-term efficacy, approval requires Opdualag to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Opdualag is recommended in those who meet the following criteria:

FDA-Approved Indication

178. Melanoma. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 12 years of age; AND
- **B)** Patient is ≥ 40 kg; AND
- **C)** Patient has unresectable or metastatic disease; AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Opdualag is not recommended in the following situations:

274. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

850. Opdualag intravenous infusion [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; March 2022.
851. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 21, 2023. Search term: nivolumab and relatlimab.
852. The NCCN Melanoma: Cutaneous Clinical Practice Guidelines in Oncology (version 2.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 21, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable – Programmed Death Receptor-1) – Zynyz Prior Authorization Policy
- Zynyz™ (retifanlimab-dlwr intravenous infusion – Incyte)

REVIEW DATE: 03/29/2023, selected revision 04/19/2023

OVERVIEW

Zynyz, a programmed death receptor-1 blocking antibody, is indicated for the treatment of metastatic or recurrent locally advanced **Merkel cell carcinoma** in adults.[1]

Guidelines

The National Comprehensive Cancer Network clinical practice guidelines for **Merkel Cell Carcinoma** (version 1.2023 – April 10, 2023) recommend Zynyz as an "other recommended regimen" for the treatment of recurrent, locally advanced or regional disease (category 2A) and for disseminated disease, all in patients not amenable to surgery or radiation therapy.[2,3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zynyz. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zynyz as well as the monitoring required for adverse events and long-term efficacy, approval requires Zynyz to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zynyz is recommended in those who meet the following criteria:

FDA-Approved Indication

179. Merkel Cell Carcinoma. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following (i, ii, or iii):
  - **i.** Patient has metastatic disease; OR
  - **ii.** Patient has recurrent locally advanced disease; OR
  - **iii.** Patient has recurrent regional disease; AND
- **C)** Patient has not received prior systemic therapy for Merkel cell carcinoma; AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zynyz is not recommended in the following situations:

275. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

853. Zynyz™ intravenous infusion [prescribing information]. Wilmington, DE: Incyte; March 2023.
854. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 14, 2023. Search term: retifanlimab.
855. The NCCN Merkel Cell Carcinoma Clinical Practice Guidelines in Oncology (version 1.2023 – April 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 14, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable – Programmed Death-Ligand 1) – Bavencio Prior Authorization Policy
- Bavencio® (avelumab intravenous infusion – EMD Serono)

REVIEW DATE: 07/19/2023

OVERVIEW

Bavencio, a programmed cell death ligand-1 (PD-L1) blocking antibody, is indicated for the treatment of the following uses:[1]

- **Merkel cell carcinoma**, in patients ≥ 12 years of age with metastatic disease.
- **Renal cell carcinoma**, in combination with Inlyta® (axitinib tablets), for the first-line treatment of patients with advanced disease.
- **Urothelial carcinoma**, in patients with locally advanced or metastatic disease who have **a)** disease progression during or following platinum-containing chemotherapy; or **b)** disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; and for **c)** maintenance treatment of locally advanced or metastatic disease that has not progressed with first-line platinum-containing chemotherapy.

Guidelines

Bavencio is addressed in National Comprehensive Cancer Network (NCCN) guidelines:

- **Bladder Cancer:** Guidelines (version 3.2023 – May 25, 2023) recommend Bavencio as an alternative preferred regimen for second-line therapy (category 2A) for locally advanced or metastatic disease (Stage IV).[2,3] Guidelines also recommend Bavencio as maintenance therapy following platinum-based chemotherapy (category 1). The NCCN Compendium recommends Bavencio, as a single agent, for urothelial carcinoma of the bladder; for upper genitourinary tract tumors (metastatic disease); urothelial carcinoma of the prostate (metastatic disease); and for primary carcinoma of the urethra (recurrent or metastatic disease) as second-line or maintenance therapy.[3]
- **Gestational Trophoblastic Neoplasm:** Guidelines (version 1.2023 – December 20, 2022) recommend Bavencio as a single agent for multidrug resistant high-risk disease, and recurrent or progressive intermediate trophoblastic tumor following a platinum-containing regimen.[3,6]
- **Kidney Cancer:** Guidelines (version 1.2024 – June 21, 2023) recommend Bavencio in combination with Inlyta for first-line treatment for relapsed or Stage IV clear cell disease (category 2A).[3,5] For subsequent therapy, Bavencio + Inlyta is a category 3 recommendation.
- **Merkel Cell Carcinoma:** Guidelines (version 1.2023 – April 10, 2023) recommend Bavencio as one of the options for disseminated disease (category 2A).[3,4] Clinical trial is preferred in this setting; but other PD-1/PD-L1 inhibitor options for disseminated disease include Keytruda® (pembrolizumab intravenous infusion) and Opdivo® (nivolumab intravenous infusion) [all category 2A].
- **Uterine Neoplasms:** Guidelines (version 2.2023 – April 28, 2023) recommend Bavencio, as a single agent, for the treatment of recurrent or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors.[3,7]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Bavencio. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Bavencio, as well as the monitoring required for adverse events and long-term efficacy, approval requires Bavencio to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Bavencio is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Merkel Cell Carcinoma.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   A) Patient is ≥ 12 years of age; AND
   B) Patient has metastatic (disseminated) Merkel cell carcinoma; AND
   C) The medication is prescribed by or in consultation with an oncologist.

2. **Renal Cell Carcinoma.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has relapsed or Stage IV clear cell disease; AND
   C) The medication will be used in combination with Inlyta (axitinib tablets); AND
   D) The medication is prescribed by or in consultation with an oncologist.

3. **Urothelial Carcinoma.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has locally advanced or metastatic urothelial carcinoma; AND
   C) Patient has tried platinum-containing chemotherapy (cisplatin or carboplatin); AND
   D) The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

4. **Endometrial Carcinoma.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has recurrent or metastatic disease; AND
   C) Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors; AND
   D) The medication will be used as a single agent; AND
   E) The medication is prescribed by or in consultation with an oncologist.

5. **Gestational Trophoblastic Neoplasia.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has multi-agent chemotherapy resistant disease; AND
   C) The medication will be used as a single agent; AND
   D) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Bavencio is not recommended in the following situations:

136. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

11. Bavencio® intravenous infusion [prescribing information]. Rockland, MA: EMD Serono; July 2021.
12. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – May 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 10, 2023.
13. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 10, 2023. Search term: avelumab.
14. The NCCN Merkel Cell Carcinoma Clinical Practice Guidelines in Oncology (version 1.2023 – April 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 10, 2023.
15. The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (version 1.2024 – June 21, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 10, 2023.
16. The NCCN Gestational Trophoblastic Neoplasia Clinical Practice Guidelines in Oncology (version 1.2023 – December 20, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 10, 2023.
17. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (version 2.2023 – April 28, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 10, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable – Programmed Death-Ligand 1) – Imfinzi Prior Authorization Policy
- Imfinzi® (durvalumab intravenous infusion – AstraZeneca)

REVIEW DATE: 07/19/2023; selected revision 10/25/2023

OVERVIEW

Imfinzi, a programmed cell death ligand 1 (PD-L1) blocking antibody, is indicated for the following uses:[1]

- **Biliary tract cancers**, in combination with gemcitabine and cisplatin for the treatment locally advanced or metastatic disease in adults.
- **Hepatocellular carcinoma**, in combination with Imjudo® (tremelimumab-actl intravenous infusion) for the treatment of unresectable disease in adults.
- **Non-small cell lung cancer (NSCLC)**, in adults with unresectable Stage III disease that has not progressed following concurrent platinum-based chemotherapy and radiation therapy.
- **NSCLC**, in adults with metastatic disease with no sensitizing epidermal growth factor receptor (*EGFR*) mutations or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations, in combination with Imjudo and platinum-based chemotherapy.
- **Small cell lung cancer**, in combination with etoposide and either carboplatin or cisplatin for the first-line treatment of extensive-stage disease in adults.

Guidelines

Imfinzi is addressed in National Comprehensive Cancer Network guidelines:

- **Ampullary Adenocarcinoma:** Guidelines (version 1.2023 – April 27, 2023) recommend Imfinzi for the first-line treatment of pancreatobiliary/mixed type disease in patients with unresectable localized disease or metastatic disease.[2,8]
- **Biliary Tract Cancers:** Guidelines (version 2.2023 – May 10, 2023) recommend Imfinzi for the primary and subsequent treatment of unresectable or metastatic biliary tract cancers and for the neoadjuvant treatment of resectable locally advanced gallbladder disease, in combination with cisplatin and gemcitabine.[2,7]
- **Cervical Cancer:** Guidelines (version 1.2023 – January 6, 2023) recommend Imfinzi, in combination with etoposide and either cisplatin or carboplatin for the treatment of persistent, recurrent, or metastatic small cell neuroendocrine carcinoma of the cervix.[2,5]
- **Esophageal and Esophagogastric Junction Cancers:** The guidelines (version 3.2023 – August 29, 2023) recommend Imfinzi in combination with Imjudo for the neoadjuvant treatment of microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) adenocarcinoma in patients who are medically fit for surgery.[2,9]
- **Gastric Cancer:** The guidelines (version 2.2023 – August 29, 2023) recommend Imfinzi in combination with Imjudo for the neoadjuvant treatment of microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) locoregional disease in patients who are medically fit for surgery.[2,10]
- **Hepatocellular Carcinoma:** Guidelines (version 1.2023 – March 10, 2023) recommend Imfinzi, as monotherapy or in combination with Imjudo, as first-line treatment of hepatocellular carcinoma in patients with unresectable disease who are not transplant candidates, in patients who are inoperable due to performance status or comorbidities, and with metastatic disease.[2,5] Imfinzi is also recommended for the primary and subsequent treatment of unresectable or metastatic biliary tract cancers in combination with cisplatin and gemcitabine.

- **Non-Small Cell Lung Cancer:** Guidelines (version 3.2023 – April 13, 2023) recommend Imfinzi as consolidation therapy for patients with unresectable stage II (category 2A) or stage III (category 1) disease with a performance status of 0 or 1 and no disease progression following definitive chemoradiation.[2,3] The guidelines recommend Imfinzi for the first-line treatment of recurrent, advanced, or metastatic disease with PD-L1 expression ≥ 1% and negative for actionable molecular markers. The guidelines also recommend Imfinzi for disease with PD-L1 expression < 1%, and for disease that is positive for a variety of molecular markers.
- **Small Cell Lung Cancer:** Guidelines (version 3.2023 – December 21, 2022) recommend Imfinzi in combination with etoposide and carboplatin/cisplatin as a "Preferred" primary treatment, followed by Imfinzi as single-agent maintenance therapy (category 1) for patients with extensive stage disease.[2,4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Imfinzi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Imfinzi, as well as the monitoring required for adverse events and long-term efficacy, approval requires Imfinzi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Imfinzi is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Biliary Tract Cancer.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Patient has resectable locally advanced disease: Approve for a 6 months (total) if the patient meets ALL of the following (i, ii, iii, iv, and v):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has gallbladder cancer; AND
     - **iii.** The medication is used as neoadjuvant therapy; AND
     - **iv.** The medication is used in combination with cisplatin and gemcitabine; AND
     - **v.** The medication is prescribed by or in consultation with an oncologist; OR
   - **B)** Patient has unresectable, recurrent, or metastatic disease: Approve for 1 year if the patient meets ALL of the following (i, ii, iii, iv, and v):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** If the patient has recurrent disease, recurrence occurred at least 6 months after surgery and at least 6 months after adjuvant therapy; AND
     - **iii.** Patient has ONE of the following (a, b, or c):
       - **a)** Gallbladder cancer; OR
       - **b)** Intrahepatic cholangiocarcinoma; OR
       - **c)** Extrahepatic cholangiocarcinoma; AND
     - **iv.** The medication will be used in combination with cisplatin and gemcitabine; AND
     - **v.** The medication is prescribed by or in consultation with an oncologist.
   - **A)**

2. **Hepatocellular Carcinoma.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets ONE of the following (i or ii):
      i. Patient has unresectable or metastatic disease; OR
      ii. According to the prescriber, the patient is not a surgical candidate; AND
   C) The medication will be used first-line; AND
   D) Patient meets ONE of the following (i or ii):
      i. The medication is used as monotherapy; OR
      ii. The medication is used in combination with Imjudo (tremelimumab-actl intravenous infusion); AND
   E) The medication is prescribed by or in consultation with an oncologist.

3. **Non-Small Cell Lung Cancer.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   B) Patient has unresectable Stage II or III disease: Approve for 1 year (total) of therapy if the patient meets ALL of the following (i, ii, and iii):
      i. Patient is ≥ 18 years of age; AND
      ii. Patient has not had disease progression following treatment with concurrent platinum-based chemotherapy and radiation therapy; AND
      iii. The medication is prescribed by or in consultation with an oncologist; OR
   C) Patient has recurrent, advanced, or metastatic disease: Approve for 1 year if the patient meets ONE of the following (i, ii, iii, or iv):
      i. Patient meets ALL of the following (a, b, c, and d):
         a) Patient is ≥ 18 years of age; AND
         b) The tumor is negative for actionable molecular markers; AND
            A) Note: Examples of actionable molecular markers include epidermal growth factor receptor (*EGFR*) mutations, anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations, *KRAS*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET*, *RET*, and *ERBB2* (*HER2*).
         c) Patient meets ONE of the following [(1) or (2)]:
            (1) Imfinzi is used as first-line therapy; OR
            (2) Imfinzi is used as continuation maintenance therapy; AND
         d) The medication is prescribed by or in consultation with an oncologist; OR
      ii. Patient meets ALL of the following (a, b, c, and d):
         a) Patient is ≥ 18 years of age; AND
         b) The tumor is positive for ONE of the following [(1), (2), or (3)]:
            (1) Epidermal growth factor receptor (*EGFR*) exon 20 mutation positive; OR
            (2) *KRAS G12C* mutation positive; OR
            (3) *ERBB2* (*HER2*) mutation positive; AND
         c) Imfinzi is used as first-line therapy; AND
         d) The medication is prescribed by or in consultation with an oncologist; OR
      iii. Patient meets ALL of the following (a, b, c, and d):
         a) Patient is ≥ 18 years of age; AND
         b) The tumor is positive for ONE of the following [(1), (2), (3), or (4)]:
            (1) *BRAF V600E* mutation positive; OR
            (2) *NTRK1/2/3* gene fusion positive; OR
            (3) *MET* exon 14 skipping mutation positive; OR
            (4) *RET* rearrangement positive; AND
         c) Imfinzi is used as first-line or subsequent therapy; AND
         d) The medication is prescribed by or in consultation with an oncologist; OR

iv. Patient meets ALL of the following (a, b, c, d, and e):
- **a)** Patient is ≥ 18 years of age; AND
- **b)** The tumor is positive for ONE of the following [(1), (2), (3), or (4)]:
  - **(1)** *EGFR* exon 19 deletion or exon 21 *L858R* mutation positive; OR
  - **(2)** *EGFR S768I*, *L861Q*, and/or *G719X* mutation positive; OR
  - **(3)** *ALK* rearrangement positive; OR
  - **(4)** *ROS1* rearrangement; AND
- **c)** The patient has received targeted drug therapy for the specific mutation; AND
  Note: Examples of targeted drug therapy include Gilotrif (afatinib tablets), Tagrisso (osimertinib tablets), erlotinib, Iressa (gefitinib tablets), Xalkori (crizotinib capsules), Zykadia (ceritinib capsules), Alecensa (alectinib capsules), Alunbrig (brigatinib tablets), Lorbrena (lorlatinib tablets), Rozlytrek (entrectinib capsules), or Vizimpro (dacomitinib tablets).
- **d)** Imfinzi is used as subsequent therapy; AND
- **e)** Imfinzi is prescribed by or in consultation with an oncologist.

D)

4. **Small Cell Lung Cancer.** Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has extensive stage disease; AND
   - **C)** Patient meets ONE of the following (i or ii):
     - **i.** The medication is used in combination with etoposide and platinum chemotherapy; OR
       E) Note: Examples of platinum chemotherapy agents include cisplatin and carboplatin.
     - **ii.** The medication is used as a single-agent for maintenance after chemotherapy; AND
   - **D)** The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

5. **Ampullary Adenocarcinoma.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E, and F):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has pancreatobiliary/mixed type disease; AND
   - **C)** Patient has unresectable localized disease or metastatic disease; AND
   - **D)** The medication is used as first-line therapy; AND
   - **E)** The medication is used in combination with gemcitabine and cisplatin; AND
   - **F)** The medication is prescribed by or in consultation with an oncologist.

6. **Cervical Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has small cell neuroendocrine carcinoma of the cervix; AND
   - **C)** Patient has persistent, recurrent, or metastatic disease; AND
   - **D)** The medication is used in combination with etoposide and platinum chemotherapy; AND
     F) Note: Examples of platinum chemotherapy agents include cisplatin and carboplatin
   - **E)** The medication is prescribed by or in consultation with an oncologist.

7. **Esophageal and Esophagogastric Junction Cancers**. Approve for 3 months if the patient meets ALL of the following (A, B, C, D, E, F, and G):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has adenocarcinoma tumor; AND

C) Patient has microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) disease; AND
D) Imfinzi is as neoadjuvant therapy; AND
E) Imfinzi is used in combination with Imjudo (tremelimumab intravenous infusion); AND
F) According to the physician, the patient is medically fit for surgery; AND
G) The medication is prescribed by or in consultation with an oncologist.

8. Gastric Cancer. Approve for 3 months if the patient meets ALL of the following (A, B, C, D, E, F, and G):
A) Patient is ≥ 18 years of age; AND
B) Patient has locoregional disease; AND
C) Patient has microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) disease; AND
D) Imfinzi is as neoadjuvant therapy; AND
E) Imfinzi is used in combination with Imjudo (tremelimumab intravenous infusion); AND
F) According to the physician, the patient is medically fit for surgery; AND
G) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Imfinzi is not recommended in the following situations:

137. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

18. Imfinzi® intravenous infusion [prescribing information]. Wilmington, DE: AstraZeneca; June 2023.
19. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 10, 2023. Search term: durvalumab.
20. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – April 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 11, 2023.
21. The NCCN Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – December 21, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 10, 2023.
22. The NCCN Hepatocellular Carcincoma Clinical Practice Guidelines in Oncology (version 1.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 11, 2023.
23. The NCCN Cervical Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – January 6, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 11, 2023.
24. The NCCN Biliary Tract Cancers Clinical Practice Guidelines in Oncology (version 2.2023 – May 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 11, 2023.
25. The NCCN Ampullary Adenocarcinoma Clinical Practice Guidelines in Oncology (version 1.2023 – April 27, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 11, 2023.
26. The NCCN Esophageal and Esophagogastric Junction Cancers Clinical Practice Guidelines in Oncology (version 3.2023 – August 29, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed October 23, 2023.
27. The NCCN Gastric Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – August 29, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed October 23, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable – Programmed Death-Ligand 1) – Tecentriq Prior Authorization Policy
- Tecentriq® (atezolizumab intravenous infusion – Genentech/Roche)

REVIEW DATE: 12/20/2023

OVERVIEW

Tecentriq, a programmed death-ligand 1 (PD-L1) blocking antibody, is indicated for the treatment of the following:[1]

- **Alveolar Soft Part Sarcoma**, in patients ≥ 2 years of age with unresectable or metastatic disease.
- **Hepatocellular carcinoma**, in combination with bevacizumab, for the treatment of unresectable or metastatic hepatocellular carcinoma in adults who have not received prior systemic therapy.
- **Melanoma**, in combination with Cotellic® (cobimetinib tablets) and Zelboraf® (vemurafenib tablets), for the treatment of *BRAF V600* mutation-positive unresectable or metastatic disease in adults.
- **Non-small cell lung cancer** (NSCLC), **metastatic** disease in adults:
  - As a single agent, as adjuvant treatment following resection and platinum-based chemotherapy for adults with Stage II to IIIA disease whose tumors express PD-L1 on ≥ 1% of tumor cells.
  - As a single agent, for the first-line treatment of tumors with high PD-L1 expression (PD-L1 staining ≥ 50% of tumor cells or PD-L1 staining of tumor infiltrating immune cells covering ≥ 10% of the tumor area), for adults with no anaplastic lymphoma kinase (*ALK*) or epidermal growth factor receptor (*EGFR*) genomic tumor aberrations.
  - In combination with bevacizumab, paclitaxel, and carboplatin, in adults for the first-line treatment of metastatic non-squamous NSCLC with no *ALK* or *EGFR* genomic tumor aberrations.
  - In combination with paclitaxel protein-bound and carboplatin, in adults for the first-line treatment of non-squamous metastatic NSCLC with no *ALK* or *EGFR* genomic tumor aberrations.
  - As a single-agent, in adults who have disease progression during or following platinum-containing chemotherapy. Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Tecentriq.
- **Small cell lung cancer** in adults, in combination with carboplatin and etoposide, for the first-line treatment of adults with extensive-stage disease.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tecentriq. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tecentriq as well as the monitoring required for adverse events and long-term efficacy, approval requires the medication to be prescribed by or in consultation with a prescriber who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tecentriq is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Alveolar Soft Part Sarcoma.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   A) Patient is ≥ 2 years of age; AND
   B) Patient has unresectable or metastatic disease; AND
   C) The medication is used as a single agent; AND
   D) The medication is prescribed by or in consultation with an oncologist.
   3.
2. **Hepatocellular Carcinoma.** Approve for 1 year if the patient meets the following (A, B, C, D, E, F, and G):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets ONE of the following (i or ii):
      i. Patient has unresectable or metastatic hepatocellular carcinoma; OR
      ii. According to the prescriber, the patient is not a surgical candidate; AND
   C) Patient has Child-Pugh Class A or B liver function; AND
   D) According to the prescriber, the patient has ONE of the following (i, ii, or iii):
      i. Unresectable disease and is not a transplant candidate; OR
      ii. Liver-confined disease, inoperable by performance status, comorbidity, or with minimal or uncertain extrahepatic disease; OR
      iii. Metastatic disease or extensive liver tumor burden; AND
         E) Patient has not received prior systemic therapy; AND
         F) The medication will be used in combination with bevacizumab; AND
         G) The medication is prescribed by or in consultation with an oncologist.

4. **Melanoma.** Approve for 1 year if the patient meets the following (A, B, C, D, E, and F):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has unresectable or metastatic melanoma; AND
   C) Patient has *BRAF V600* mutation-positive disease; AND
   D) The medication will be used as subsequent therapy; AND
   E) The medication will be used in combination with Cotellic (cobimetinib tablets) and Zelboraf (vemurafenib tablets); AND
   F) The medication is prescribed by or in consultation with an oncologist.

5. **Non-Small Cell Lung Cancer.** Approve for the duration noted if the patient meets the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets one of the following (i, ii, iii, iv, or v):
      i. Approve for 1 year if the patient has non-squamous non-small cell lung cancer (NSCLC) and the patient meets all of the following (a, b, and c):

   CCCC) Note: Non-squamous NSCLC includes adenocarcinoma, large cell, or NSCLC not otherwise specified.
      a) Patient has recurrent, advanced, or metastatic disease; AND
      b) The tumor is negative for actionable mutations; AND

   DDDD) Note: Examples of actionable mutations include epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *ROS1*, *KRAS*, *BRAF V600E*, *NRTK1/2/3*, *MET* exon 14 skipping mutation, *RET* rearrangement.
      c) Patient meets one of the following [(1), (2), or (3)]:

(1) Patient's tumor expresses programmed death-ligand 1 (PD-L1) ≥ 1% as determined by an approved test; OR

EEEE) Note: In this setting Tecentriq can be used either as a single agent or in combination with other agents.

(2) The medication will be used in combination with chemotherapy; OR

FFFF) Note: Examples of chemotherapy regimens may include bevacizumab, paclitaxel, and carboplatin; carboplatin and paclitaxel albumin-bound intravenous infusion.

(3) The medication is used as continuation maintenance therapy; OR

GGGG) Note: Tecentriq can be used in combination with bevacizumab or as single agent in this setting.

ii. Approve for 1 year if the patient has squamous cell NSCLC and meets all of the following (a, b, and c):

a) Patient has recurrent, advanced, or metastatic disease; AND

b) The tumor is negative for actionable mutations; AND

HHHH) Note: Examples of actionable mutations include epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *ROS1*, *KRAS*, *BRAF V600E, NRTK1/2/3, MET* exon 14 skipping mutation, *RET* rearrangement.

c) Patient's tumor expresses programmed death-ligand 1 (PD-L1) ≥ 50% as determined by an approved test; OR

iii. Approve for 1 year if the patient has recurrent, advanced, or metastatic non-squamous cell NSCLC and meets one of the following (a, b, or c):

a) Patient meets all of the following [(1), (2), and (3)]:

(1) The tumor is epidermal growth factor receptor (*EGFR*) exon 20 mutation positive, *KRAS G12C* mutation positive, or *ERBB2* (*HER2*) mutation positive; AND

(2) The medication is used first-line; AND

(3) The medication is used in combination with chemotherapy; OR

IIII) Note: Examples of chemotherapy include carboplatin, paclitaxel, and bevacizumab; and carboplatin plus paclitaxel albumin-bound.

b) Patient meets all of the following [(1), (2), and (3)]:

(1) The tumor is *BRAF V600E* mutation positive, *NTRK1/2/3* gene fusion positive, *MET* exon 14 skipping mutation positive, or *RET* rearrangement positive; AND

(2) The medication is used for first-line or subsequent treatment; AND

(3) The medication is used in combination with chemotherapy; OR

JJJJ) Note: Examples of chemotherapy include carboplatin, paclitaxel, and bevacizumab; and carboplatin plus paclitaxel albumin-bound.

c) Patient meets all of the following [(1), (2), and (3)]:

(1) The tumor is epidermal growth factor receptor (*EGFR*) exon 19 deletion or exon 21 *L858R* positive, *EGFR S768I*, *L861Q*, and/or *G719X* mutation positive, *ALK* rearrangement positive, or *ROS1* rearrangement positive; AND

(2) Patient has received targeted drug therapy for the specific mutation; AND

(3) The medication is used in combination with chemotherapy; OR

KKKK) Note: Examples of chemotherapy include carboplatin, paclitaxel, and bevacizumab; and carboplatin plus paclitaxel albumin-bound.

iv. Approve for 1 year if the patient meets all of the following (a, b, c, and d):

a) Patient has recurrent, advanced, or metastatic disease; AND

b) The medication is used as subsequent therapy; AND

c) The medication is used as a single agent; AND

d) The patient has not progressed on a programmed death receptor-1 (PD-1) or programmed death-ligand 1 inhibitor (PD-L1); OR

LLLL) Note: Examples of PD-1 or PD-L1 inhibitors include Tecentriq, Keytruda (pembrolizumab intravenous infusion), and Opdivo (nivolumab intravenous infusion).

v. Approve for up to 1 year (total) if the patient meets both of the following (a and b):

a) Patient's tumor expresses programmed death-ligand 1 (PD-L1) ≥ 1% as determined by an approved test; AND

b) Patient has received previous adjuvant chemotherapy; AND

C) The medication is prescribed by or in consultation with an oncologist.

MMMM)

5. **Small Cell Lung Cancer.** Approve for 1 year if the patient meets both of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

6. **Cervical Cancer.** Approve for 1 year if the patient meets the following (A, B, C, D, and E):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has small cell neuroendocrine carcinoma of the cervix; AND
   C) Patient has persistent, recurrent, or metastatic disease; AND
   D) The medication is used in combination with chemotherapy; AND
   6. Note: Examples of chemotherapy include cisplatin or carboplatin, with etoposide.
   E) The medication is prescribed by or in consultation with an oncologist.

7. **Mesothelioma.** Approve for 1 year if the patient meets the following (A, B, C, D, and E):
   I) Patient is ≥ 18 years of age; AND
   J) The medication is used as subsequent therapy; AND
   K) The medication is used in combination with bevacizumab; AND
   L) Patient has ONE of the following (i, ii, or iii):
   i. Malignant peritoneal mesothelioma; OR
   ii. Pericardial mesothelioma; OR
   iii. Tunica vaginalis testis mesothelioma; AND
   M) The medication is prescribed by or in consultation with an oncologist.
   NNNN)

8. **Urothelial Carcinoma.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   A) Patient is ≥ 18 years of age; AND
   B) Patient is currently receiving Tecentriq for the treatment of urothelial carcinoma; AND
   C) According to the prescriber, the patient is deriving benefit from Tecentriq; AND
   D) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tecentriq is not recommended in the following situations:

138. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

436. Tecentriq® intravenous infusion [prescribing information]. South San Francisco, CA: Genentech; May 2023.

437. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 13, 2023. Search term: atezolizumab.
438. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 3.2023 – December 12, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed December 18, 2023.
439. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 5.2023 – November 8, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 18, 2023.
440. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – May 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 13, 2023.
441. The NCCN Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 2.2024 – November 21, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 13, 2023.
442. The NCCN Hepatocellular Carcinoma Clinical Practice Guidelines in Oncology (version 2.2023 – September 14, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 13, 2023.
443. The NCCN Melanoma: Cutaneous Clinical Practice Guidelines in Oncology (version 3.2023 – October 27, 2023). © 2023 National Comprehensive Cancer Network. Available at: www.nccn.org. Accessed on December 13, 2023.
444. The NCCN Mesothelioma: Peritoneal Clinical Practice Guidelines in Oncology (version 1.2024 – November 21, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed December 13, 2023.
445. The NCCN Cervical Cancer Clinical Practice Guidelines in Oncology (version 1.2024 – September 20, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed December 18, 2023.

OOOO)

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Adcetris Prior Authorization Policy
- Adcetris® (brentuximab intravenous infusion – Seattle Genetics)

REVIEW DATE: 10/11/2023

OVERVIEW

Adcetris, a CD30 directed antibody conjugate, is indicated for the following uses:[1]

- **Classical Hodgkin lymphoma**:
  - **A)** In adults with previously untreated Stage III or IV disease, in combination with doxorubicin, vinblastine, and dacarbazine.
  - **B)** In adults at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation consolidation.
  - **C)** After failure of autologous hematopoietic stem cell transplantation or after failure of at least two prior multi-agent chemotherapy regimens in adults who are not autologous hematopoietic stem cell transplantation candidates.
  - **D)** In patients ≥ 2 years of age with previously untreated, high risk disease in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide.
- **Primary cutaneous anaplastic large cell lymphoma** or **CD30-expressing mycosis fungoides**, in adults who have received prior systemic therapy.
- **Systemic anaplastic large cell lymphoma** or other **CD30-expressing peripheral T-cell lymphomas**, including angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphomas not otherwise specified, in previously untreated adults in combination with cyclophosphamide, doxorubicin, and prednisone.
- **Systemic anaplastic large cell lymphoma**, in adults who have failed at least one prior multi-agent chemotherapy regimen.

Guidelines

Adcetris is addressed in National Comprehensive Cancer Network (NCCN) guidelines:

- **B-Cell Lymphomas:** Guidelines for adults (version 5.2023 – July 7, 2023) recommend Adcetris for second-line or subsequent treatment of CD30+ diffuse large B-cell lymphoma (DLBCL), CD30+ high-grade B-cell lymphoma, CD30+ human immunodeficiency virus (HIV)-related B-cell lymphoma, and CD30+ post-transplant lymphoproliferative disorders.[2,6] Pediatric guidelines (version 1.2023 – April 4, 2023) recommend Adcetris for consolidation/additional therapy if partial response is achieved after therapy for relapsed or refractory disease.[2,8] While these guidelines recommend Adcetris for the treatment of primary mediastinal B-cell lymphoma, the study cited by NCCN to support this indication only included patients > 18 years of age.[9] The median age in this study was 35.5 years (range: 19 to 83 years).
- **Hodgkin Lymphoma**: Guidelines for adults (version 2.2023 – November 8, 2022) recommend Adcetris for the treatment of classical Hodgkin Lymphoma in combination with chemotherapy, as primary treatment, second-line or subsequent therapy for relapsed or refractory disease, as maintenance therapy following high-dose therapy and autologous stem cell rescue for relapsed or refractory disease, or as palliative therapy.[2,3] Pediatric guidelines (version 2.2023 – March 9, 2023) recommend Adcetris for primary and additional treatment of high risk disease; re-induction or subsequent therapy for relapsed or refractory disease in heavily pretreated patients or patients with reduced cardiac function in combination with bendamustine, Opdivo® (nivolumab intravenous

infusion), and gemcitabine; and as maintenance therapy following high-dose therapy and autologous stem cell rescue.[2,7]

- **T-Cell Lymphomas**: Guidelines (version 2.2022 – March 7, 2022) recommend Adcetris as a first-line or subsequent treatment option for a variety of CD30+ T-cell lymphomas, either as a single agent or in combination with cyclophosphamide, doxorubicin, and prednisone.[2,4] Primary cutaneous lymphomas guidelines (version 1.2023 – Janury 5, 2023) recommend Adcetris for the systemic therapy of CD30+: mycosis fungoides/Sezary syndrome, primary cutaneous anaplastic large cell lymphoma, and lymphomatoid papulosis.[2,5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Adcetris. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Adcetris as well as the monitoring required for adverse events and long-term efficacy, approval requires Adcetris to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Adcetris is recommended in those who meet one of the following criteria:

FDA-Approved Indications

6. **Hodgkin Lymphoma.** Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient has classical Hodgkin lymphoma; AND
   - **B)** The medication is prescribed by or in consultation with an oncologist.

7. **T-Cell Lymphoma**. Approve for 1 year if the patient meets the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Adcetris is used for CD30+ T-cell lymphoma; AND
     Note: Examples include CD30+ systemic anaplastic large cell lymphoma, CD30+ angioimmunoblastic T-cell lymphoma, CD30+ peripheral T-cell lymphoma not otherwise specified, CD30+ mycosis fungoides/Sezary syndrome, CD30+ primary cutaneous anaplastic large cell lymphoma, CD30+ lymphomatoid papulosis, CD30+ breast implant-associated anaplastic large cell lymphoma, CD30+ adult T-cell leukemia/lymphoma, CD30+ hepatosplenic T-cell lymphoma, CD30+ extranodal NK/T-cell lymphoma.
   - **C)** The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

8. **B-Cell Lymphoma**. Approve for 1 year if the patient meets the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Adcetris is used as second-line or subsequent therapy for CD30+ B-cell lymphoma; AND
     Note: Examples include CD30+ diffuse large B-cell lymphoma, CD30+ post-transplant lymphoproliferative disorders, CD30+ HIV-related B-cell lymphoma, CD30+ high-grade B-cell lymphoma, CD30+ primary mediastinal large B-cell lymphoma.
   - **C)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Adcetris is not recommended in the following situations:

276. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

856. Adcetris® intravenous infusion [prescribing information]. Bothell, WA: Seattle Genetics; June 2023.
857. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 2, 2023. Search term: brentuximab.
858. The NCCN Hodgkin Lymphoma Clinical Practice Guidelines in Oncology (version 2.2023 – November 8, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 2, 2023.
859. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 2, 2023.
860. The NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 2, 2023.
861. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 5.2023 – July 7, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 2, 2023.
862. The NCCN Pediatric Hodgkin Lymphoma Clinical Practice Guidelines in Oncology (version 3.2023 – March 9, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 2, 2023.
863. The NCCN Pediatric Aggressive Mature B-Cell Lymphoma Clinical Practice Guidelines in Oncology (version 1.2023 – April 4, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 2, 2023.
864. Zinzani PL, Santoro A, Gritti G, et al. Nivolumab combined with brentuximab vedotin for relapsed/refractory primary mediastinal large B-cell lymphoma: Efficacy and safety from the Phase II CheckMate 436 study. *J Clin Oncol.* 2019;37:3081-3089.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Aliqopa Prior Authorization Policy
- Aliqopa® (copanlisib intravenous infusion – Bayer)

REVIEW DATE: 09/06/2023

OVERVIEW

Aliqopa, a kinase inhibitor, is indicated for the treatment of relapsed **follicular lymphoma** in adults who have received at least two prior systemic therapies.[1]

Guidelines

The National Comprehensive Cancer Network guidelines on **B-Cell Lymphomas** (version 5.2023 – July 7, 2023) recommend Aliqopa as a third-line agent and subsequent therapy for relapsed/refractory follicular lymphoma (grade 1 or 2), extranodal marginal zone lymphoma of the stomach, extranodal marginal zone lymphoma of nongastric sites, splenic marginal zone lymphoma, and nodal marginal zone lymphoma.[2,3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Aliqopa. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Aliqopa as well as the monitoring required for adverse events and long-term efficacy, approval requires Aliqopa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Aliqopa is recommended in those who meet one of the following criteria:

FDA-Approved Indication

9. Follicular Lymphoma. Approve for 1 year if the patient meets the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has received ≥ 2 prior systemic therapies; AND

  Note: Examples of systemic therapies include bendamustine, cyclophosphamide, doxorubicin, vincristine, rituximab product (e.g., Rituxan, biosimilars), Gazyva (obinutuzumab intravenous infusion).
- **C)** Aliqopa is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

10. Marginal Zone Lymphoma. Approve for 1 year if the patient meets the following (A, B, and C):
Note: This includes extranodal marginal zone lymphoma of the stomach, extranodal marginal zone lymphoma of nongastric sites, nodal marginal zone lymphoma, and splenic marginal zone lymphoma.
A) Patient is ≥ 18 years of age; AND
B) Patient has received ≥ 2 prior systemic therapies; AND
Note: Examples of systemic therapies include bendamustine, cyclophosphamide, doxorubicin, vincristine, rituximab product (e.g., Rituxan, biosimilars), Gazyva (obinutuzumab intravenous infusion).
C) Aliqopa is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Aliqopa is not recommended in the following situations:

277. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

865. Aliqopa® intravenous infusion [prescribing information]. Whippany, NJ: Bayer; March 2023.
866. The NCCN B-Cell Lymphoma Clinical Practice Guidelines in Oncology (version 5.2023 – July 7, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed August 30, 2023.
867. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on August 30, 2023. Search term: copanlisib.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Arsenic Trioxide Prior Authorization Policy
- Trisenox® (arsenic trioxide intravenous infusion – Teva, generic)

REVIEW DATE: 10/11/2023

OVERVIEW

Arsenic trioxide is indicated for **acute promyelocytic leukemia (APL)**:[1]

- In combination with tretinoin for the treatment of adults with newly diagnosed low-risk disease whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression.
- For induction of remission and consolidation in patients with APL who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression.

Guidelines

Arsenic trioxide is addressed in National Comprehensive Cancer Network (NCCN) Guidelines.

- **Acute Myeloid Leukemia:** Guidelines (version 4.2023 – July 11, 2023) recommend arsenic trioxide for induction and consolidation therapy in low-risk (white blood cell [WBC] count < 10,000/µL) and in high-risk (WBC > 10,000/µL) APL with or without cardiac issues.[2,3] NCCN also recommends arsenic trioxide for the first relapse (either morphologic or molecular) and as single-agent consolidation therapy in patients who are not transplant candidates and are polymerase chain reaction negative following second remission (morphologic).
- **T-Cell Lymphoma:** Guidelines (version 1.2023 – January 5, 2023) recommend arsenic trioxide as a single agent for the second-line or subsequent treatment of non-responders to first-line therapy for adult T-cell leukemia/lymphoma, acute or lymphoma subtypes.[2,4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of arsenic trioxide. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with arsenic trioxide as well as the monitoring required for adverse events and long-term efficacy, approval requires arsenic trioxide to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of arsenic trioxide is recommended in those who meet one of the following criteria:

FDA-Approved Indication

11. Acute Promyelocytic Leukemia. Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

12. Adult T-Cell Leukemia/Lymphoma. Approve for 1 year if the patient meets the following (A, B, C, D, and E):

A) Patient is ≥ 18 years of age; AND

B) Patient has acute or lymphoma subtype; AND

C) Patient has tried chemotherapy; AND

Note: Examples include CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone).

D) Arsenic trioxide will be used as a single agent; AND

E) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of arsenic trioxide is not recommended in the following situations:

278. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

868. Trisenox® intravenous infusion [prescribing information]. North Wales, PA: Teva; October 2022.
869. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 2, 2023. Search term: arsenic trioxide.
870. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 4.2023 – July 11, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 2, 2023.
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PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Asparlas Prior Authorization Policy
- Asparlas™ (calaspargase pegol-mknl intravenous infusion – Servier)

REVIEW DATE: 12/21/2022

OVERVIEW

Asparlas is indicated as a component of a multi-agent chemotherapy regimen for the treatment of **acute lymphoblastic leukemia** (ALL) in pediatric and young adults, age 1 month to 21 years.[1]

Asparlas is a conjugate of L-asparaginase, produced by *E. coli*, and monomethoxypolyethylene glycol (mPEG) with a succinimidyl carbonate linker.[1] The succinimidyl carbonate linker forms a stable chemical bond between mPEG and L-asparaginase. Asparlas catalyzes the conversion of L-asparagine into aspartic acid and ammonia. Leukemia cells with low expression of asparagine synthetase cannot make L-asparagine and require exogenous sources for survival. Asparlas kills leukemia cells by depleting the plasma of exogenous L-asparagine.

Guidelines

The National Comprehensive Cancer Network clinical practice guidelines for ALL (version 1.2022 – April 4, 2022) state that Asparlas can be substituted for pegaspargase in patients ≤ 21 years of age and the Pediatric ALL (version 1.2023 – November 9, 2022) state that Asparlas can be substituted for pegaspargase in patients aged 1 month to 21 years, for more sustained asparaginase activity.[2-4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Asparlas. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Asparlas as well as the monitoring required for adverse events and long-term efficacy, approval requires Asparlas to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Asparlas is recommended in those who meet the following criteria:

FDA-Approved Indication

3. Acute Lymphoblastic Leukemia. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient is 1 month to 21 years of age; AND
- **B)** Asparlas is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Asparlas is not recommended in the following situations:

279. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

872. Asparlas™ [prescribing information]. Boston, MA: Servier Pharmaceuticals; December 2021.
873. The NCCN Drugs & Biologics Compendium. © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 15, 2022. Search term: calaspargase.
874. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 1.2022 – April 4, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 15, 2022.
875. The NCCN Pediatric Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 1.2023 – November 9, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 15, 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Azedra Prior Authorization Policy
- Azedra® (iobenguane I 131 intravenous infusion – Progenics)

REVIEW DATE: 10/11/2023

OVERVIEW

Azedra, a radioactive therapeutic agent, is indicated for the treatment of adult and pediatric patients ≥ 12 years of age with **iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma** who require systemic anticancer therapy.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for Neuroendocrine and Adrenal Tumors (version 1.2023 – August 2, 2023) note surgical resection as the mainstay of treatment for benign and malignant pheochromocytomas and paragangliomas.[2] For locally unresectable tumors, observation is recommended if the patient is asymptomatic or has slow-growing, low-volume disease. For patients with locally unresectable or distant metastatic pheochromocytoma or paraganglioma, primary treatment for secreting tumors that are positive on metaiodobenzylguanidine (MIBG) scan include Azedra or other I-131 MIBG therapy (category 2A).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Azedra. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Azedra as well as the monitoring required for adverse events and long-term efficacy, approval requires Azedra to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Azedra is recommended in those who meet one of the following criteria:

FDA-Approved Indications

64. Pheochromocytoma. Approve Azedra for 6 months if the patient meets the following (A, B, C, D, and E):
- **C)** Patient is ≥ 12 years of age; AND
- **D)** Patient has iobenguane scan positive pheochromocytoma; AND
- **E)** The tumor is unresectable; AND
- **F)** The tumor is locally advanced or metastatic; AND
- **G)** The medication is prescribed by or in consultation with an oncologist or radiologist.

65. Paraganglioma. Approve Azedra for 6 months if the patient meets the following (A, B, C, D, and E):
- **B)** Patient is ≥ 12 years of age; AND
- **C)** Patient has iobenguane scan positive paraganglioma; AND

D) The tumor is unresectable; AND
E) The tumor is locally advanced or metastatic; AND
F) The medication is prescribed by or in consultation with an oncologist or radiologist.

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CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Azedra is not recommended in the following situations:

139. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Azedra® I 131 intravenous infusion [prescribing information]. New York, NY: Progenics Pharmaceuticals; March 2021.
2. The NCCN Neuroendocrine and Adrenal Tumors Clinical Practice Guidelines in Oncology (version 1.2023 – August 2, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 4, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Beleodaq Prior Authorization Policy
- Beleodaq® (belinostat intravenous infusion – Spectrum)

REVIEW DATE: 09/06/2023

OVERVIEW

Beleodaq, a histone deacetylase inhibitor, is indicated for the treatment of relapsed or refractory **peripheral T-cell lymphoma** in adults.[1]

Guidelines

Beleodaq is addressed in the National Comprehensive Cancer Network (NCCN) **T-Cell Lymphomas** guidelines (version 1.2023 – January 5, 2023). NCCN recommends Beleodaq as a single-agent for second-line and subsequent therapy of peripheral T-cell lymphoma, breast implant-associated anaplastic large cell lymphoma, adult T-cell leukemia/lymphoma, extranodal NK/T-cell lymphoma, and hepatosplenic T-cell lymphoma.[2,3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Beleodaq. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Beleodaq as well as the monitoring required for adverse events and long-term efficacy, approval requires Beleodaq to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Beleodaq is recommended in those who meet the following criteria:

FDA-Approved Indication

2. T-Cell Lymphoma. Approve for 1 year if Beleodaq is prescribed by or in consultation with an oncologist or a dermatologist.
Note: Examples include peripheral T-cell lymphoma, breast implant-associated anaplastic large cell lymphoma, adult T-cell leukemia/lymphoma, hepatosplenic T-cell lymphoma, extranodal NK/T-cell lymphoma.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Beleodaq is not recommended in the following situations:

280. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

876. Beleodaq® intravenous infusion [prescribing information]. Irvine, CA: Spectrum Pharmaceuticals; April 2022.
877. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed August 31, 2023.
878. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on August 31, 2023. Search term: belinostat.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Bendamustine Products Prior Authorization Policy
- Belrapzo™ (bendamustine intravenous infusion – Eagle)
- Bendeka® (bendamustine intravenous infusion – Teva)
- Treanda® (bendamustine intravenous infusion – Cephalon)
- Bendamustine intravenous infusion – various manufacturers

REVIEW DATE: 07/12/2023

OVERVIEW

Bendamustine, an alkylating agent, is indicated for the following uses:[1-3]
- **B-cell non-Hodgkin lymphoma, indolent**, that has progressed during or within 6 months of treatment with rituximab or a rituximab containing regimen.
- **Chronic lymphocytic leukemia**. Efficacy compared to first-line agents other than chlorambucil has not been established.

Guidelines

Bendamustine is addressed in National Comprehensive Cancer Network guidelines:
- **B-Cell Lymphomas**: Guidelines (version 4.2023 – June 2, 2023) recommend bendamustine for the treatment of a variety B-cell lymphomas, including follicular lymphoma (grade 1 and 2), gastric extranodal marginal zone lymphoma of the stomach, extranodal marginal zone lymphoma of nongastric sites, nodal marginal zone lymphoma, splenic marginal zone lymphoma, histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, DLBCL, high-grade B-cell lymphoma, human immunodeficiency virus (HIV)-related B-cell lymphoma, and post-transplant lymphoproliferative disorders.[4,6] Bendamustine is recommended as monotherapy, or in combination with rituximab (e.g., Rituxan, biosimilars), Polivy™ (polatuzumab vedotin-piiq intravenous [IV] infusion), or Gazyva® (obinutuzumab IV infusion) depending on the lymphoma type and previous treatment .
- **Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma**: Guidelines (version 3.2023 – June 12, 2023) recommend bendamustine, in combination with rituximab or Gazyva, for the first-line treatment of patients without del(17p)/TP53 mutation, who have indications for treatment (not recommended for frail patients).[4,5] Bendamustine in combination with rituximab is recommended for the treatment of relapsed or refractory disease without del(17p)/TP53 mutation in patients ≥ 65 years of age, or in patients < 65 years of age with or without significant comorbidities.
- **Hematopoietic Cell Transplantation**: Guidelines (version 1.2023 – March 31, 2023) recommend bendamustine in combination with etoposide, cytarabine, and melphalan as a conditioning regimen for autologous transplantation for patients with non-Hodgkin lymphoma without central nervous system disease, or Hodgkin lymphoma.[4,13]
- **Hodgkin Lymphoma** and **Pediatric Hodgkin Lymphoma**: Guidelines for Hodgkin lymphoma (version 2.2023 – November 8, 2023) and pediatric Hodgkin lymphoma (version 2.2023 – March 9, 2023) recommend bendamustine for the treatment of recurrent or refractory Hodgkin lymphoma.[4,7,11] In patients ≥ 18 years of age with classic Hodgkin lymphoma, bendamustine in combination with gemcitabine and vinorelbine, or in combination with Adcetris® (brentuximab IV infusion) is recommended for second-line or subsequent therapy (if not previously used), or in combination with carboplatin and etoposide for third-line or subsequent therapy, or as a single agent for subsequent therapy. In patients ≥ 18 years of age with nodular lymphocyte-predominant Hodgkin lymphoma, bendamustine in combination with rituximab is recommended for the

subsequent treatment of progressive, relapsed, or refractory disease. In patients > 60 years of age, bendamustine is recommended as a single agent for palliative therapy of relapsed or refractory disease. For heavily pretreated pediatric patients with Hodgkin lymphoma, bendamustine in combination with Adcetris is recommended for re-induction or subsequent treatment of relapsed or refractory disease.

- **Multiple Myeloma**: Guidelines (version 3.2023 – December 8, 2022) recommend bendamustine as a treatment option for late relapsed or progressive multiple myeloma (patient has received > 3 prior therapies).[4,8] Bendamustine is recommended as a single agent, or in combination with dexamethasone and lenalidomide, with dexamethasone and bortezomib, or with dexamethasone and Kyprolis® (carfilzomib intravenous infusion).
- **Systemic Light Chain Amyloidosis**: Guidelines (version 2.2023 – November 28, 2022) recommend bendamustine in combination with dexamethasone for relapsed/refractory disease.[4,12]
- **T-Cell Lymphomas**: Guidelines (version 1.2023 – January 5, 2023) recommend bendamustine as a single agent for the treatment of relapsed or refractory peripheral T-cell lymphomas, breast implant-associated anaplastic large cell lymphoma, adult T-cell leukemia/lymphoma, and refractory hepatosplenic T-cell lymphoma as subsequent therapy.[4,9]
- **Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma**: Guidelines (version 1.2023 – July 6, 2022) recommend bendamustine as a single agent or in combination with rituximab for primary treatment, for the treatment of previously treated disease that did not respond, or for progressive or relapsed disease.[4,10]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of bendamustine. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with bendamustine as well as the monitoring required for adverse events and long-term efficacy, approval requires bendamustine to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of bendamustine is recommended in those who meet one of the following criteria:

FDA-Approved Indications

4. **B-Cell Non-Hodgkin Lymphoma.** Approve for 6 months if the patient meets BOTH of the following (A and B):
   Note: Examples include follicular lymphoma, extranodal marginal zone lymphoma of the stomach, extranodal marginal zone lymphoma of nongastric sites, nodal marginal zone lymphoma, splenic marginal zone lymphoma, histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma (DLBCL), DLBCL, and high-grade B-cell lymphoma.
   A) Patient is ≥ 18 years of age; AND
   B) Bendamustine is prescribed by or in consultation with an oncologist.

5. **Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma.** Approve for 6 months if the patient meets BOTH of the following (A and B):
   A) Patient is ≥ 18 years of age; AND

B) Bendamustine is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

6. Hematopoietic Cell Transplantation. Approve for 1 month if the patient meets ALL of the following (A, B, and C):
- **A)** Bendamustine is used as conditioning prior to autologous hematopoietic cell transplantation; AND
- **B)** Patient has ONE of the following conditions (i or ii):
  - **i.** Non-Hodgkin lymphoma without central nervous system disease; OR
  - **ii.** Hodgkin lymphoma; AND
- **C)** Bendamustine is prescribed by or in consultation with an oncologist or a physician who specializes in hematopoietic cell transplantation.

7. Hodgkin Lymphoma. Approve for 6 months if the patient meets BOTH of the following (A and B):
- **A)** Bendamustine is used as second-line or subsequent therapy; AND
- **B)** Bendamustine is prescribed by or in consultation with an oncologist.

8. Multiple Myeloma. Approve for 6 months if the patient meets ALL of the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has been treated with more than 3 prior regimens; AND
- **C)** Bendamustine is prescribed by or in consultation with an oncologist.

9. Systemic Light Chain Amyloidosis. Approve for 6 months if the patient meets ALL of the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has relapsed or refractory disease; AND
- **C)** Bendamustine is used in combination with dexamethasone; AND
- **D)** Bendamustine is prescribed by or in consultation with an oncologist.

10. T-Cell Lymphoma. Approve for 6 months if the patient meets ALL of the following (A, B, and C):
Note: Examples include peripheral T-cell lymphoma, breast implant-associated anaplastic large cell lymphoma, adult T-cell leukemia/lymphoma, hepatosplenic T-cell lymphoma.
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Bendamustine is used as a single agent; AND
- **C)** Bendamustine is prescribed by or in consultation with an oncologist.

11. Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma. Approve for 6 months if the patient meets BOTH of the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Bendamustine is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of bendamustine is not recommended in the following situations:

281. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

879. Bendeka® intravenous infusion [prescribing information]. North Wales, PA: Teva; October 2021.
880. Treanda® intravenous infusion [prescribing information]. Frazer, PA: Cephalon; June 20219.
881. Belrapzo™ intravenous infusion [prescribing information]. Woodcliff Lake, NJ: Eagle Pharmaceuticals; June 2022.

882. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 26, 2023. Search term: bendamustine.
883. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (version 3.2023 – June 12, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 26, 2023.
884. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 4.2023 – June 2, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 26, 2023.
885. The NCCN Hodgkin Lymphoma Clinical Practice Guidelines in Oncology (version 2.2023 – November 8, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 26, 2023.
886. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 3.2023 – December 8, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 26, 2023.
887. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 26, 2023.
888. The NCCN Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma Clinical Practice Guidelines in Oncology (version 1.2023 – July 6, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 26, 2023.
889. The NCCN Pediatric Hodgkin Lymphoma Clinical Practice Guidelines in Oncology (version 2.2023 – March 9, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 26, 2023.
890. The NCCN Systemic Light Chain Amyloidosis Clinical Practice Guidelines in Oncology (version 2.2023 – November 28, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 26, 2023.
891. The NCCN Hematopoietic Cell Transplantation (HCT) Clinical Practice Guidelines in Oncology (version 1.2023 – March 31, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 26, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Besponsa Prior Authorization Policy
- Besponsa® (inotuzumab ozogamicin intravenous infusion – Pfizer)

REVIEW DATE: 07/12/2023

OVERVIEW
Besponsa, an antibody-drug conjugate directed against human CD22, is indicated for the treatment of adults with relapsed or refractory B-cell precursor **acute lymphoblastic leukemia** (ALL).[1]

Guidelines
Besponsa is addressed in National Comprehensive Cancer Network (NCCN) guidelines:
- **ALL:** Guidelines (version 1.2023 – May 31, 2023) recommend Besponsa for the frontline treatment of relapsed/refractory Philadelphia chromosome negative (Ph-) B-cell ALL, or relapsed/refractory Ph- B-cell ALL or Philadelphia chromosome positive (Ph+) B-cell ALL, as a single agent or in combination with mini-hyper CVD (cyclophosphamide, dexamethasone, vincristine, methotrexate, cytarabine).[2,3] For Ph+ B-cell ALL only, guidelines recommend Besponsa in combination with a tyrosine kinase inhibitor. Besponsa is also recommended for induction therapy for Ph- B-cell ALL in patients ≥ 65 years of age or in patients with substantial comorbidities in combination with mini-hyper CVD.
- **Pediatric ALL:** Guidelines (version 2.2023 – March 10, 2023) for pediatric patients recommend Besponsa as a single-agent or in combination with mini-hyper-CVD for the treatment of relapsed/refractory Ph- B-cell ALL, or relapsed/refractory Ph+ B-cell ALL with tyrosine kinase inhibitor intolerant or refractory disease.[3,4]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Besponsa. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Besponsa as well as the monitoring required for adverse events and long-term efficacy, approval requires Besponsa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Besponsa is recommended in those who meet the following criteria:

FDA-Approved Indication

3. **Acute Lymphoblastic Leukemia.** Approve for 6 months if the patient meets the following (A and B):
Note: This applies to Philadelphia chromosome positive and negative acute lymphoblastic leukemia.
- **D)** Patient has B-cell precursor acute lymphoblastic leukemia; AND
- **E)** Besponsa is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Besponsa is not recommended in the following situations:

282. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

892. Besponsa® intravenous infusion [prescribing information]. Philadelphia, PA: Pfizer; March 2018.
893. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 1.2023 – May 31, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 27, 2023.
894. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 27, 2023. Search term: inotuzumab.
895. The NCCN Pediatric Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 2.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed June 26, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Besremi Prior Authorization Policy
- Besremi® (ropeginterferon alfa-2b-njft subcutaneous injection – PharmaEssentia)

REVIEW DATE: 11/15/2023

OVERVIEW
Besremi, an interferon alfa-2b, is indicated for treatment of adults with **polycythemia vera**.[1]

Guidelines
The National Comprehensive Cancer Network guidelines for myeloproliferative neoplasms (version 3.2023 – October 25, 2023) discuss therapies for polycythemia vera.[2] In low-risk patients, management of cardiovascular risk factors, low-dose aspirin (81 to 100 mg/day), and phlebotomy to maintain hematocrit < 45% are recommended (category 2A for all). Besremi, hydroxyurea, and Pegasys® (peginterferon alfa-2a subcutaneous injection) are listed as a "preferred" regimens for symptomatic low-risk polycythemia vera (category 2A). In high-risk patients, "preferred" regimens for cytoreductive therapy include hydroxyurea, Pegasys, and Besremi [category 2A for all]. Besremi can also be used if the patient has an inadequate response or loss of response to hydroxyurea or interferons, if not previously used. A footnote states that Pegasys is an option for younger patients or in pregnant patients in need of cytoreductive therapy for both low-risk and high-risk disease.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Besremi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Besremi as well as the monitoring required for adverse events and long-term efficacy, approval requires Besremi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Besremi is recommended in those who meet the following criteria:

FDA-Approved Indication

13. Polycythemia Vera. Approve for 1 year the patient meets the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Besremi is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Besremi is not recommended in the following situations:

283. Concomitant Use with Other Interferon Products. Besremi was not studied in combination with other interferon products; concomitant use would be expected to result in increased toxicity.

Note: An example of an interferon product is Pegasys® (peginterferon alfa-2a subcutaneous injection).

284. Hepatitis B Virus. Besremi is not indicated for hepatitis B.[1] Pegylated interferons are recommended in American Association for the Study of Liver Diseases (AASLD) guidelines for chronic hepatitis B (updated 2018).[3] Phase I/II data suggest similar efficacy between Besremi and Pegasys for chronic hepatitis B; however, further data are needed.[4]

285. Hepatitis C Virus. Besremi is not indicated for hepatitis C.[1] Pegasys, another pegylated interferon, is indicated for the treatment of chronic hepatitis C. However, peginterferons are no longer addressed by the AASLD recommendations for testing, managing, and treating HCV (updated October 24, 2022).[5]

286. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

896. Besremi® subcutaneous injection [prescribing information]. Burlington, MA: PharmaEssentia; November 2021.
897. The NCCN Myeloproliferative Neoplasms Clinical Practice Guidelines in Oncology (version 3.2023 – October 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 14, 2023.
898. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018 Apr;67(4):1560-1599.
899. Huang YW, Hsu CW, Lu SN, et al. Ropeginterferon alfa-2b every 2 weeks as a novel pegylated interferon for patients with chronic hepatitis B. *Hepatol Int*. 2020 Dec;14(6):997-1008.
900. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. Testing, managing, and treating hepatitis C. Updated October 24, 2022. Available at: http://www.hcvguidelines.org. Accessed on: November 9, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Bevacizumab Products Prior Authorization Policy
- Avastin® (bevacizumab intravenous infusion – Genentech)
- Alymsys® (bevacizumab-maly intravenous infusion – Amneal)
- Mvasi™ (bevacizumab-awwb intravenous infusion – Amgen)
- Vegzelma™ (bevacizumab-adcd intravenous infusion – Celltrion)
- Zirabev™ (bevacizumab-bvzr intravenous infusion – Pfizer)

REVIEW DATE: 03/22/2023

OVERVIEW

Bevacizumab is a recombinant humanized monoclonal antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF), a key mediator of angiogenesis.[1] Bevacizumab is indicated for the following uses:

- **Cervical cancer**, in combination with paclitaxel and cisplatin OR paclitaxel and topotecan for persistent, recurrent, or metastatic disease.
- **Colorectal cancer**, metastatic:
  - In combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment.
  - In combination with fluoropyrimidine-irinotecan-based or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab-containing regimen.
  - **i.** Limitation of use: Bevacizumab is not indicated for adjuvant treatment of colon cancer.
- **Glioblastoma**, for treatment of recurrent disease in adults.
- **Hepatocellular carcinoma**, in combination with Tecentriq® (atezolizumab intravenous infusion) for the treatment of unresectable or metastatic disease in patients who have not received prior systemic therapy.
- **Non-small cell lung cancer (NSCLC)**, for non-squamous disease, in combination with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent, or metastatic disease.
- **Ovarian (epithelial), fallopian tube, or primary peritoneal cancer:**
  - Recurrent disease that is platinum-resistant in combination with paclitaxel, Doxil® (doxorubicin liposome intravenous infusion), or topotecan, in patients who received no more than two prior chemotherapy regimens.
  - Recurrent disease that is platinum-sensitive in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by bevacizumab as a single agent.
  - In combination with carboplatin and paclitaxel, followed by bevacizumab as a single agent, for stage III or IV disease in patients following initial surgical resection.
- **Renal cell carcinoma**, metastatic, in combination with interferon alfa.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of bevacizumab for uses other than ophthalmic conditions. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with bevacizumab as well as the monitoring required for adverse events and long-term efficacy, approval requires bevacizumab to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of bevacizumab products is recommended in those who meet one of the following criteria:

FDA-Approved Indications

29. Central Nervous System Tumors. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
Note: For pediatric patients see Pediatric Central Nervous System Tumors.
a. Patient is ≥ 18 years of age; AND
b. Patient has tried at least one previous therapy; AND
ii. Note: Examples are temozolomide capsules or injection, etoposide, carmustine, radiotherapy.
c. Patient has ONE of the following (i, ii, iii, iv, v, vi, or vii):
i. Anaplastic gliomas; OR
ii. Astrocytoma; OR
iii. Glioblastoma; OR
iv. Intracranial and spinal ependymoma (excluding subependymoma); OR
v. Meningiomas; OR
vi. Oligodendroglioma; OR
vii. Symptoms due to one of the following (a, b, or c):
a) Radiation necrosis; OR
b) Poorly controlled vasogenic edema; OR
c) Mass effect; AND
d. The medication is prescribed by or in consultation with an oncologist.

30. Cervical Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
N) Patient is ≥ 18 years of age; AND
O) Patient meets ONE of the following (i or ii):
i. Patient has recurrent or metastatic cervical cancer; OR
ii. Patient has persistent, recurrent, or metastatic small cell neuroendocrine carcinoma of the cervix; AND
P) The medication is prescribed by or in consultation with an oncologist.

31. Colon, Rectal, or Appendiceal Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has recurrent, advanced, or metastatic colon, rectal, or appendiceal cancer; AND
C) The medication is used in combination with a chemotherapy regimen; AND
Note: Examples of chemotherapy are 5-fluorouracil with leucovorin, and may include one or both of oxaliplatin, irinotecan; capecitabine with or without oxaliplatin; irinotecan with or without oxaliplatin.
D) The medication is prescribed by or in consultation with an oncologist.

32. Hepatocellular Carcinoma. Approve for 1 year if the patient meets the following criteria (A, B, C, D, E, and F):
A) Patient is ≥ 18 years of age; AND

B) Patient meets ONE of the following (i or ii):
i. Patient has unresectable or metastatic hepatocellular carcinoma; OR
ii. According to the prescriber, the patient in not a surgical candidate; AND
C) Patient has Child-Pugh Class A disease; AND
D) The medication is used in combination with Tecentriq (atezolizumab intravenous infusion); AND
E) Patient has not received prior systemic therapy; AND
F) The medication is prescribed by or in consultation with an oncologist.

33. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient does not have a of recent hemoptysis; AND
C) Patient has recurrent, advanced, or metastatic non-squamous non-small cell lung cancer (NSCLC) and meets ONE of the following criteria (i, ii, iii, iv, or v):
Note: Non-squamous NSCLC includes adenocarcinoma, large cell, or NSCLC not otherwise specified.
i. The NSCLC tumor is negative or unknown for actionable mutations and the patient meets ONE of the following criteria (a, b, or c):
Note: Examples of actionable mutations include sensitizing epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *RET* rearrangement positive, *MET* exon 14 skipping, *NTRK* gene fusion positive, *BRAF V600E* mutation positive, and ROS proto-oncogene 1 (*ROS1*) rearrangement positive.
a) The medication is used as initial therapy in combination with other systemic therapies; OR
iii. Note: Examples of systemic therapies are cisplatin, carboplatin, Tecentriq (atezolizumab intravenous infusion), pemetrexed, paclitaxel.
b) The medication is used as continuation maintenance therapy and meets ONE of the following [(1), (2), or (3)]:
(1) The medication is used as a single agent; OR
(2) The medication is used in combination with Tecentriq, if Tecentriq was used in combination with bevacizumab for first-line therapy; OR
(3) The medication is used in combination with pemetrexed, if pemetrexed was used in combination with bevacizumab for first-line therapy; OR
c) The medication is used as subsequent therapy in combination with other systemic therapies; OR
iv. Note: Examples of systemic therapies are cisplatin, carboplatin, pemetrexed, paclitaxel.
ii. The tumor is positive for *EGFR* exon 19 deletion or exon 21 *L858R* mutations and the patient meets ONE of the following (a or b):
a) The medication is used as first-line or continuation maintenance therapy in combination with erlotinib; OR
b) The medication is used as subsequent therapy following prior targeted therapy; OR
v. Note: Examples of targeted therapy include Gilotrif (afatinib tablet), Tagrisso (osimertinib tablet), erlotinib, Iressa (gefitinib tablet), Vizimpro (dacomitinib tablet).
iii. Patient meets all of the following (a, b, and c):
a) The medication is used first-line; AND
b) The medication is used in combination with other systemic therapies;
vi. Note: Examples include carboplatin plus paclitaxel or pemetrexed, cisplatin plus pemetrexed, and Tecentriq plus carboplatin and paclitaxel.
c) The tumor is positive for ONE of the following mutations [(1), (2), or (3)]:

(1) *EGFR* exon 20 mutation; OR
(2) *KRAS G12C* mutation; OR
(3) *ERBB2* (HER2) mutation; OR

iv. Patient meets all of the following (a, b, and c):
a) The medication is used as first-line or subsequent therapy; AND
b) The medication is used in combination with other systemic therapies; AND
vii. Note: Examples include carboplatin plus paclitaxel or pemetrexed, cisplatin plus pemetrexed, and Tecentriq plus carboplatin and paclitaxel.
c) The tumor is positive for ONE of the following mutations [(1), (2), (3), or (4)]:
(1) *BRAF V600E* mutation; OR
(2) *NTRK1/2/3* gene fusion positive; OR
(3) *MET* exon 14 skipping mutation; OR
(4) *RET* rearrangement positive; OR

v. Patient meets all of the following (a, b, c, and d):
a) The medication is used as subsequent therapy; AND
b) The medication is used in combination with other systemic therapies; AND
viii. Note: Examples include carboplatin plus paclitaxel or pemetrexed, cisplatin plus pemetrexed, and Tecentriq plus carboplatin and paclitaxel.
c) The tumor is positive for ONE of the following mutations [(1), (2), or (3)]
(1) *EGFR S768I, L861Q*, and/or *G719X* mutation; OR
(2) *ALK* rearrangement positive; OR
(3) *ROS1* rearrangement positive; AND
d) Patient has previously received targeted drug therapy for the specific mutation; AND
ix. Note: Examples of targeted drug therapy include Gilotrif (afatinib tablet), Tagrisso (osimertinib tablet), erlotinib, Iressa (gefitinib tablet), Vizimpro (dacomitinib tablet), Xalkori (crizotinib capsule), Rozlytrek (entrectinib capsule), or Zykadia (ceritinib tablet).

D) The medication is prescribed by or in consultation with an oncologist.

6. Ovarian, Fallopian Tube, or Primary Peritoneal Cancer. Approve for 1 year if the patient meets the following criteria (A and B):
A) Patient is ≥ 18 years of age; AND
B) The medication is prescribed by or in consultation with an oncologist.

7. Renal Cell Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patient has relapsed, metastatic, or stage IV renal cell cancer; AND
C) The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

8. Ampullary Adenocarcinoma. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has intestinal type disease; AND
C) The medication is used in combination with chemotherapy; AND
x. Note: Examples of chemotherapy include FOLFOX (leucovorin, fluorouracil, oxaliplatin), FOLFIRI (leucovorin, fluorouracil, irinotecan), FOLFOXIRI (leucovorin, fluorouracil, oxaliplatin, irinotecan), and CapeOX (capecitabine, oxaliplatin).
D) The medication is prescribed by or in consultation with an oncologist.

9. **Endometrial Carcinoma.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has recurrent, advanced, or metastatic disease; AND
   C) The medication is prescribed by or in consultation with an oncologist.
   xi.
10. **Mesothelioma.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has one of the following (i, ii, iii, or iv):
      i. Malignant pleural mesothelioma; OR
      ii. Malignant peritoneal mesothelioma; OR
      iii. Pericardial mesothelioma; OR
      iv. Tunica vaginalis testis mesothelioma; AND
   C) Patient meets ONE of the following (i or ii):
      i. Bevacizumab will be used in combination with a chemotherapy regimen; OR
      xii. Note: Examples of chemotherapy are pemetrexed, cisplatin, carboplatin.
      ii. Bevacizumab will be used in combination with Tecentriq (atezolizumab intravenous infusion); AND
   D) The medication is prescribed by or in consultation with an oncologist.
   xiii.
11. **Neovascular or Vascular Ophthalmic Conditions.** Approve for 3 years.
   xiv. Note: Examples of neovascular or vascular ophthalmic conditions include diabetic macular edema (includes patients with diabetic retinopathy and diabetic macular edema), macular edema following retinal vein occlusion, myopic choroidal neovascularization, neovascular (wet) age-related macular degeneration, other neovascular diseases of the eye (e.g., neovascular glaucoma, retinopathy of prematurity, sickle cell neovascularization, choroidal neovascular conditions).

12. **Pediatric Central Nervous System Tumors.** Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
   A) Patient is < 18 years of age; AND
   B) Patient has pediatric-type diffuse high-grade glioma; AND
   xv. Note: Examples include diffuse hemispheric glioma, diffuse pediatric-type high-grade glioma, infant-type hemispheric glioma, and diffuse midline glioma.
   C) Patient has recurrent or progressive disease; AND
   D) The medication is used for palliation; AND
   E) The medication is prescribed by or in consultation with an oncologist.
   xvi.
13. **Small Bowel Adenocarcinoma.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has advanced or metastatic disease; AND
   C) The medication is used in combination with chemotherapy; AND
   xvii. Note: Examples of chemotherapy are fluorouracil, leucovorin, and oxaliplatin (FOLFOX), capecitabine and oxaliplatin (CapeOX), fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI).
   D) The medication is prescribed by or in consultation with an oncologist.
   xviii.
14. **Soft Tissue Sarcoma.** Approve for 1 year if the patient meets BOTH of the following criteria (A, B, and C):
   A) Patient is ≥ 18 years of age; AND

B) Patient has angiosarcoma or solitary fibrous tumor; AND
C) The medication is prescribed by or in consultation with an oncologist.
xix.

15. Vulvar Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has advanced, recurrent, or metastatic disease; AND
C) Bevacizumab is used in combination with a chemotherapy regimen; AND
xx. Note: Examples of chemotherapy regimens are cisplatin and paclitaxel, carboplatin and paclitaxel.
D) The medication is prescribed by or in consultation with an oncologist.
xxi.
xxii.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of bevacizumab products is not recommended in the following situations:

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Avastin® intravenous infusion [prescribing information]. South San Francisco, CA: Genentech. September 2022.
2. The NCCN Cervical Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – January 6, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 14, 2023.
3. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 3.2022 – January 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 15, 2023.
4. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 8, 2023. Search term: bevacizumab.
5. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 4.2022 – January 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 15, 2023.
6. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (Version 2.2022 – September 29, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 14, 2023.
7. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – February 17, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 15, 2023.
8. The NCCN Ovarian Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 15, 2023.
9. The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – January 18, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 14, 2023.
10. The NCCN Malignant Pleural Mesothelioma Clinical Practice Guidelines in Oncology (version 1.2023 – December 15, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 14, 2023.
11. The NCCN Small Bowel Adenocarcinoma Clinical Practice Guidelines in Oncology (version 1.2023 – January 9, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 14, 2023.
12. The NCCN Vulvar Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 14, 2023.
13. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 15, 2023.
14. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 2.2022 – May 17, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 14, 2023.
15. The NCCN Hepatobiliary Cancers Clinical Practice Guidelines in Oncology (version 5.2022 – January 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 15, 2023.
16. The NCCN Malignant Peritoneal Mesothelioma Clinical Practice Guidelines in Oncology (version 1.2023 – December 15, 2022). © National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 14, 2023.
17. The NCCN Pediatric Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 2.2023 – October 31, 2022). © National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 14, 2023.
18. The NCCN Ampullary Adenocarcinoma Clinical Practice Guidelines in Oncology (version 2.2022 – December 6, 2022). © National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 14, 2023.
19. Vegzelma™ intravenous infusion [prescribing information]. Incheon, South Korea: Celltrion; September 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Blenrep Prior Authorization Policy
- Blenrep™ (belantamab mafodotin-blmf intravenous infusion – GlaxoSmithKline)

REVIEW DATE: 09/27/2023

OVERVIEW

Blenrep, a B-cell maturation antigen-directed antibody and microtubule inhibitor conjugate, is indicated for treatment of adults with relapsed or refractory **multiple myeloma**, in those who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory drug. The FDA granted accelerated approval to Blenrep in August 2020, based on overall response rate from an open-label, Phase II study. Because the primary endpoint (progression-free survival) was not met in the confirmatory Phase III study, the manufacturer has initiated the process of removing Blenrep from the market. In November 2022, the manufacturer announced that no new patients would be allowed enrollment in the Blenrep REMS program.

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines for multiple myeloma (version 1.2024 – September 22, 2023) recommend various regimens as primary therapy (transplant eligible and non-transplant candidates), maintenance therapy, and previously treated multiple myeloma.[2] The choice of regimen takes into account patient factors as well as response and tolerability to previous regimens. Triplet regimens (e.g., with a proteasome inhibitor, immunomodulatory drug, and corticosteroid) are standard therapy for multiple myeloma. Blenrep is listed as useful in certain circumstances if available through the compassionate use program, and after at least four prior therapies (including an anti-CD38 monoclonal antibody, proteasome inhibitor, and an immunomodulatory drug).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Blenrep. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Blenrep as well as the monitoring required for adverse events and long-term efficacy, approval requires Blenrep to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Blenrep is recommended in those who meet the following criteria:

FDA-Approved Indication

4. Multiple Myeloma. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
- **12.** Patient is currently receiving Blenrep; AND
- **13.** Patient is ≥ 18 years of age; AND
- **14.** Patient has tried at least four systemic regimens; AND

15. Among the previous regimens tried, the patient has received at least one drug from each of the following classes (i, ii, and iii):

i. Proteasome inhibitor; AND
Note: Examples include Velcade (bortezomib injection), Kyprolis (carfilzomib infusion), Ninlaro (ixazomib capsules).

ii. Immunomodulatory drug; AND
Note: Examples include Revlimid (lenalidomide capsules), Pomalyst (pomalidomide capsules), Thalomid (thalidomide capsules).

iii. Anti-CD38 monoclonal antibody; AND
Note: Examples include Darzalex (daratumumab infusion), Darzalex Faspro (daratumumab and hyaluronidase-fihj subcutaneous injection), or Sarclisa (isatuximab-irfc infusion).

16. The medication will be prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Blenrep is not recommended in the following situations:

287. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

901. Blenrep™ intravenous infusion [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; February 2022.
902. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 1.2024 – September 22, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 25, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Blincyto Prior Authorization Policy
- Blincyto® (blinatumomab intravenous infusion – Amgen)

REVIEW DATE: 09/06/2023

OVERVIEW

Blincyto, a bispecific CD19-directed CD3 T-cell engager, is indicated for the following uses:[1]

- **Minimal residual disease (MRD)-positive, CD19-positive B-cell precursor acute lymphoblastic leukemia** (ALL) in first or second complete remission with MRD ≥ 0.1% in adults and pediatric patients.
- **Relapsed or refractory CD19-positive B-cell ALL** in adults and pediatric patients.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on **Acute Lymphoblastic Leukemia** (version 2.2023 – July 28, 2023) and **Pediatric Acute Lymphoblastic Leukemia** (version 1.2024 – August 17, 2023) recommend Blincyto for relapsed/refractory B-cell ALL; consolidation therapy in adolescents, young adults, and adults after complete response to induction therapy; maintenance therapy; and for pediatric patients with MRD positive disease, less than complete response, or for relapsed or refractory disease.[2-4]

Safety

Blincyto contains a boxed warning for cytokine release syndrome which may be life-threatening or fatal and neurologic toxicities which may be severe, life-threatening, or fatal.[1] Stop or discontinue Blincyto as recommended for either toxicity.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Blincyto. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Blincyto, as well as the monitoring required for adverse events and long-term efficacy, approval requires Blincyto to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Blincyto is recommended in those who meet the following criteria:

FDA-Approved Indication

14. Acute Lymphoblastic Leukemia. Approve for 1 year if the patient meets the following (A, B, and C):
- **F)** Patient has B-cell precursor disease; AND
- **G)** Patient meets one of the following (i, ii, or iii):
  a. Patient is Philadelphia chromosome negative and meets one of the following (a, b, c, or d):

a) Patient has relapsed or refractory disease; OR
b) Patient is minimal residual disease positive; OR
c) The medication is used for consolidation therapy; OR
d) The medication is used for maintenance therapy; OR

b. Patient is Philadelphia chromosome-like and minimal residual disease positive; OR
c. Patient is Philadelphia chromosome positive and meets one of the following (a, b, c, d, e, or f):
a) Patient has tried at least one tyrosine kinase inhibitor (TKI) used for the treatment of acute lymphoblastic leukemia; OR
Note: Examples of a TKI include imatinib tablets, Sprycel (dasatinib tablets), Tasigna (nilotinib capsules).
b) Patient has relapsed or refractory disease; OR
c) Patient does not have a complete response to induction therapy; OR
d) Patient is minimal residual disease positive; OR
e) The medication is used for consolidation therapy; OR
f) The medication is used for maintenance therapy; AND

H) Blincyto is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Blincyto is not recommended in the following situations:

288. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

903. Blincyto® intravenous infusion [prescribing information]. Thousand Oaks, CA: Amgen; June 2023.
904. The NCCN Pediatric Acute Lymphoblastic Leukemia Oncology Guidelines (version 1.2024 – August 17, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed August 31, 2023.
905. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 2.2023 – July 28, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed August 31, 2023.
906. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on August 31, 2023. Search term: blinatumomab.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Bortezomib Prior Authorization Policy
- Velcade® (bortezomib intravenous or subcutaneous injection – Takeda, generic)

REVIEW DATE: 11/15/2023

OVERVIEW

Bortezomib, a proteasome inhibitor, is indicated in adults with the following conditions:[1]

- **Mantle cell lymphoma**.
- **Multiple myeloma**.

Guidelines

Bortezomib is mentioned in several guidelines published by the National Comprehensive Cancer Network (NCCN).[2-11]

- **Acute lymphoblastic leukemia:** Guidelines for adults (version 3.2023 – October 9, 2023) and for pediatric patients (version 3.2024 – October 31, 2023) include bortezomib + chemotherapy among the other recommended regimens for relapsed or refractory disease.[3,4]
- **B-cell lymphomas:** Guidelines (version 6.2023 – October 10, 2023) recommend bortezomib (as a component of (VR-CAP [bortezomib/rituximab/cyclophosphamide/ doxorubicin/prednisone]) as a preferred less aggressive therapy option for the initial treatment of patients (induction therapy) with newly diagnosed mantle cell lymphoma.[5] Bortezomib ± rituximab is also listed as second-line and subsequent therapy for relapsed or refractory mantle cell lymphoma. For patients with relapsed or refractory multicentric Castleman's disease, bortezomib ± rituximab is listed among the treatment options.
- **Kaposi sarcoma:** Guidelines (version 1.2024 – November 7, 2023) include bortezomib among the subsequent systemic therapy options for patients who have relapsed or refractory disease.[6]
- **Classic Hodgkin lymphoma:** Guidelines for pediatric disease (version 2.2023 – March 9, 2023) include bortezomib/ifosfamide/vinorelbine among the subsequent therapy options for relapsed or refractory disease.[7]
- **Multiple myeloma:** Bortezomib features prominently in the NCCN Multiple Myeloma clinical practice guidelines (version 2.2024 – November 1, 2023).[8] Bortezomib-containing regimens are listed as preferred for primary therapy (transplant and nontransplant candidates) and previously treated disease. Bortezomib is also a component of multiple other regimens across the spectrum of disease. For maintenance therapy, bortezomib ± lenalidomide capsules (and ± dexamethasone for transplant candidates) are also listed as treatment options.
- **Systemic light chain amyloidosis:** Guidelines (version 1.2024 – October 18, 2023) list bortezomib alone or in combination with other agents for primary therapy (transplant and non-transplant candidates) and previously treated disease.[9] NCCN notes that bortezomib was well tolerated at doses up to 1.6 mg/m^2 on a once-weekly schedule and 1.3 mg/m^2 on a twice-weekly schedule. The once-weekly regimen was associated with lower neurotoxicity.
- **T-cell lymphomas:** Guidelines (version 1.2023 – January 5, 2023) recommend bortezomib (category 2A) as an alternative regimen for second-line or subsequent therapy.[11]
- **Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma:** Guidelines (version 1.2024 – September 28, 2023) recommend bortezomib/dexamethasone/rituximab as a preferred regimen for primary therapy and for previously treated disease.[10]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of bortezomib. All approvals are provided for the duration noted below. Because of the of the specialized skills required for evaluation and diagnosis of patients treated with bortezomib, as well as the monitoring required for adverse events and long-term efficacy, approval requires bortezomib to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of bortezomib is recommended in those who meet one of the following criteria:

FDA-Approved Indications

5. **Mantle Cell Lymphoma.** Approve for 1 year if the patient meets the following (A, B, and C):
   a. Patient is ≥ 18 years of age; AND
   b. Patient meets ONE of the following (i or ii):
      i. Patient has previously tried at least one other therapy for mantle cell lymphoma; OR
      Note: Examples of other therapies for mantle cell lymphoma include regimens containing a rituximab product, cytarabine, cisplatin, cyclophosphamide, doxorubicin, vincristine, or bendamustine.
      ii. The medication is used in combination with at least one other agent; AND
      Note: Examples of other agents used in combination with bortezomib for mantle cell lymphoma include a rituximab product, bendamustine, cyclophosphamide, and doxorubicin.
   c. The medication is prescribed by or in consultation with an oncologist or a hematologist.

6. **Multiple Myeloma.** Approve for 1 year if the patient meets the following (A, B, and C):
   17. Patient is ≥ 18 years of age; AND
   18. Patient meets ONE of the following (i or ii):
      i. The medication will be used in combination with at least one other agent; OR
      Note: Examples of other agents that may be used in combination with bortezomib include dexamethasone, cyclophosphamide, doxorubicin, Doxil (doxorubicin liposomal intravenous infusion), Revlimid (lenalidomide capsules), Thalomid (thalidomide capsules), cisplatin, etoposide, Darzalex (daratumumab intravenous infusion), Pomalyst (pomalidomide capsules), bendamustine, Empliciti (elotuzumab intravenous infusion), Farydak (panobinostat capsules).
      ii. The medication is being used for maintenance therapy; AND
   19. The medication is prescribed by or in consultation with an oncologist or a hematologist.

Other Uses with Supportive Evidence

7. **Acute Lymphoblastic Leukemia.** Approve for 1 year if the patient meets the following (A and B):
   a. Patient has relapsed or refractory disease; AND
   b. The medication is prescribed by or in consultation with an oncologist.

8. **Castleman's Disease.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   a. Patient is ≥ 18 years of age; AND
   b. Patient has multicentric Castleman's disease; AND
   c. Patient has relapsed, refractory, or progressive disease; AND
   d. The medication is prescribed by or in consultation with an oncologist.

9. **Classic Hodgkin Lymphoma.** Approve for 1 year if the patient meets the following (A and B):
   a. Patient has tried at least one systemic chemotherapy regimen; AND
      Note: Examples of systemic chemotherapies used in regimens for Hodgkin lymphoma include doxorubicin, bleomycin, vincristine, etoposide, and dacarbazine.
   b. The medication is prescribed by or in consultation with an oncologist.

10. **Kaposi Sarcoma.** Approve for 1 year if the patient meets the following (A, B, and C):
   a. Patient is ≥ 18 years of age; AND
   b. Patient has tried at least one systemic chemotherapy; AND
      Note: Examples of systemic chemotherapies include doxorubicin and paclitaxel.
   c. The medication is prescribed by or in consultation with an oncologist.

11. **Systemic Light Chain Amyloidosis.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) The medication is prescribed by or in consultation with an oncologist or a hematologist.

12. **T-Cell Lymphoma**. Approve for 1 year if the patient meets the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has tried at least one systemic therapy; AND
      Note**:** Examples of systemic therapies include EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), Adcetris (brentuximab vedotin) + CHP (cyclophosphamide, doxorubicin, and prednisone), zidovudine + interferon, CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone), HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytrarabine.
   C) The medication is prescribed by or in consultation with an oncologist.

13. **Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma.** Approve for 1 year if the patient meets the following (A, B, and C):
   a. Patient is ≥ 18 years of age; AND
   b. The medication will be used in combination with rituximab and dexamethasone; AND
   c. The medication is prescribed by or in consultation with an oncologist or a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of bortezomib is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Velcade® subcutaneous injection or intravenous infusion [prescribing information]. Lexington, MA: Takeda; November 2021.
2. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 13, 2023. Search term: bortezomib.
3. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 3.2023 – October 9, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 29, 2023.
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5. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 6.2023 – October 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed October 29, 2023.
6. The NCCN Kaposi Sarcoma Clinical Practice Guidelines in Oncology (version 2.2024 – November 7, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 13, 2023.
7. The NCCN Pediatric Hodgkin Lymphoma Clinical Practice Guidelines in Oncology (version 2.2023 – March 9, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 13, 2023.
8. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 2.2024 – November 1, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 13, 2023.
9. The NCCN Systemic Light Chain Amyloidosis Clinical Practice Guidelines in Oncology (version 1.2024 – October 18, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed October 29, 2023.
10. The NCCN Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma Clinical Practice Guidelines in Oncology (version 1.2024 – September 28, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed October 29, 2023.
11. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed November 13, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Carmustine Products Prior Authorization Policy
- Carmustine intravenous infusion (BICNU® – Avet, generics)

REVIEW DATE: 12/21/2022

OVERVIEW

Carmustine intravenous infusion, a nitrosourea, is approved for the following uses as a palliative agent as a single agent or in established combination therapy in the following conditions:[1]

- **Brain tumors**, including glioblastoma, brainstem glioma, medulloblastoma, astrocytoma, ependymoma, and metastatic brain tumors.
- **Hodgkin lymphoma**, in relapsed or refractory disease in combination with other approved drugs.
- **Multiple myeloma**, in combination with prednisone.
- **Non-Hodgkin lymphoma**, in relapsed or refractory disease in combination with other approved drugs.

Guidelines

Carmustine is addressed in the following National Comprehensive Cancer Network (NCCN) guidelines:

- **Central nervous system (CNS) cancers** (version 2.2022 – September 29, 2022) clinical practice guidelines support the use of carmustine injection for certain adults with recurrent or progressive low-grade glioma/pilocytic and infiltrative supratentorial astrocytoma/oligodendroglioma, and recurrent anaplastic glioma, glioblastoma, adult intracranial and spinal ependymoma (excluding subependymoma).[2,3] Carmustine injection is also part of a Preferred regimen (in combination with thiotepa) as consolidation therapy with stem cell rescue in patients with primary CNS lymphoma. The **pediatric CNS** (version 2.2023 – October 31, 2022) recommend carmustine for the palliative treatment of patients with diffuse high-grade gliomas.[3,8]
- **Hematopoietic Cell Transplantation** (version 2.2022 – September 28, 2022) clinical practice guidelines recommend carmustine as part of a conditioning regimen prior to autologous hematopoietic cell transplantation (category 2A) in patients with non-Hodgkin lymphoma, Hodgkin lymphoma, or primary CNS lymphoma.[3,7]
- **Hodgkin lymphoma** (version 2.2023 – November 8, 2022) clinical practice guidelines recommend carmustine as part of a chemotherapy regimen (e.g., MiniBEAM [carmustine/cytarabine/etoposide/melphalan]) for disease that is refractory to at least three prior lines of therapy.[3,4]

The NCCN clinical practice guidelines on **multiple myeloma** (version 3.2022 – December 8, 2022) and **B-cell lymphomas** (version 5.2022 – July 12, 2022) do not provide recommendations on the use of carmustine for the treatment of these respective indications.[5,6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of carmustine products. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with carmustine products as well as the monitoring required for adverse events and long-term efficacy, approval requires carmustine products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of carmustine intravenous infusion (BICNU, generics) is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Central Nervous System Tumor.** Approve for 1 year if the patient meets ONE of the following criteria (A or B):
   Note: Includes adult low-grade infiltrative supratentorial astrocytoma/oligodendroglioma, anaplastic gliomas, glioblastoma, adult intracranial and spinal ependymoma, primary central nervous system lymphoma, pediatric diffuse high-grade gliomas.
   - **A)** Patient is ≥ 18 years of age: Approve if the patient meets BOTH of the following (i and ii):
     - **i.** Patient meets ONE of the following (a, b, or c):
       - **a)** Patient has recurrent or progressive disease; OR
       - **b)** The medication is being used in a regimen with stem cell rescue; OR
         Note: For example, as consolidation therapy in combination with thiotepa with stem cell rescue.
       - **c)** The medication is used in place of lomustine in any PCV (procarbazine, lomustine, and vincristine) regimen; AND
     - **ii.** The medication is prescribed by or in consultation with an oncologist.
   - **B)** Patient is < 18 years of age: Approve if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient has diffuse high-grade glioma; AND
     - **ii.** The medication is used for palliative treatment; AND
     - **iii.** The medication is prescribed by or in consultation with an oncologist.

2. **Hodgkin Lymphoma.** Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has relapsed or refractory disease; AND
   - **C)** The medication is being used as part of a chemotherapy regimen; AND
     Note: For example, as a component of MiniBEAM (carmustine/cytarabine/etoposide/melphalan).
   - **D)** The medication is prescribed by or in consultation with an oncologist.

3. **Multiple Myeloma.** Approve for 1 year if the patient meets ALL of the following criteria (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** The medication is being used with prednisone; AND
   - **C)** The medication is prescribed by or in consultation with an oncologist.

4. **Non-Hodgkin Lymphoma.** Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has relapsed or refractory disease; AND
   - **C)** The medication is being used as part of a chemotherapy regimen; AND
   - **D)** The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

5. **Hematopoietic Cell Transplantation.** Approve for 1 month if the patient meets ALL of the following criteria (A, B, and C):
   A) Patient is undergoing an autologous transplant; AND
   B) The medication is being used as part of a conditioning regimen, given prior to transplantation; AND
   C) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of carmustine intravenous infusion is not recommended in the following situations:

289. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

907. BICNU [prescribing information]. East Brunswick, NJ: Avet Pharmaceuticals; November 2021.
908. The NCCN Central Nervous System Clinical Practice Guidelines in Oncology (version 2.2022 – September 29, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 15, 2022.
909. The NCCN Drugs and Biologics Compendium. © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 15, 2022. Search term: carmustine.
910. The NCCN Hodgkin Lymphoma Clinical Practice Guidelines in Oncology (version 2.2023 – November 8, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 15, 2022.
911. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 3.2023 – December 8, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 15, 2022.
912. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 5.2022 – July 12, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 15, 2022.
913. The NCCN Hematopoietic Cell Transplantation (HCT) Clinical Practice Guidelines in Oncology (version 2.2022 – September 28, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 15, 2022.
914. The NCCN Pediatric Central Nervous System Clinical Practice Guidelines in Oncology (version 2.2023 – October 31, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 15, 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Columvi Prior Authorization Policy
- Columvi™ (glofitamab-gxbm intravenous infusion – Genentech)

REVIEW DATE: 06/28/2023; selected revision 07/12/2023

OVERVIEW

Columvi, a bispecific anti-CD20-directed CD3 T-cell engager, is indicated for the treatment of **relapsed or refractory diffuse large B-cell lymphoma** (DLBCL) not otherwise specified or **large B-cell lymphoma** (LBCL) arising from follicular lymphoma, in adults after two or more lines of systemic therapy.[1]

Guidelines

The National Comprehensive Cancer Network **B-cell lymphoma** clinical practice guidelines (version 5.2023 – July 7, 2023) recommend Columvi for the third-line and subsequent treatment of DLBCL, high-grade B-cell lymphoma, histologic transformation of follicular lymphoma or nodal marginal zone lymphoma to DLBCL, human immunodeficiency virus (HIV)-related B-cell lymphoma, and post-transplant lymphoproliferative disorders.[2,3]

Safety

Columvi has a Boxed Warning for cytokine release syndrome.[1]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Columvi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Columvi as well as the monitoring required for adverse events and long-term efficacy, approval requires Columvi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Columvi is recommended in those who meet the following criteria:

FDA-Approved Indication

15. Diffuse Large B-Cell Lymphoma. Approve for 1 year if the patient meets the following (A, B, C, D, and E):

72. Note: Examples of diffuse large B-cell lymphoma (DLBCL) include DLBCL not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma or nodal marginal zone lymphoma.

A) Patient is ≥ 18 years of age; AND

B) Patient has received two or more lines of systemic therapy; AND

73. Note: Examples of systemic therapy include RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and DHA (dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) ± rituximab.

C) Medication is given as a single agent; AND
D) Patient has or will receive pretreatment with Gazyva (obinutuzumab intravenous infusion) before the first dose of Columvi; AND
E) Medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

16. Human Immunodeficiency Virus (HIV)-Related B-Cell Lymphoma. Approve for 1 year if the patient meets the following (A, B, C, D, and E):
74. Note: HIV-related B-cell lymphomas includes HIV-related diffuse large B-cell lymphoma (DLBCL), primary effusion lymphoma, and human herpes virus-8 (HHV8) positive DLBCL
A) Patient is ≥ 18 years of age; AND
B) Patient has received two or more lines of systemic therapy; AND
75. Note: Examples of systemic therapy include RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin).
C) Medication is given as a single agent; AND
D) Patient has or will receive pretreatment with Gazyva (obinutuzumab intravenous infusion) before the first dose of Columvi; AND
E) Medication is prescribed by or in consultation with an oncologist.

17. Post-Transplant Lymphoproliferative Disorders. Approve for 1 year if the patient meets the following (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has received two or more lines of systemic therapy; AND
76. Note: Examples of systemic therapy include RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine).
C) Medication is given as a single agent; AND
D) Patient has or will receive pretreatment with Gazyva (obinutuzumab intravenous infusion) before the first dose of Columvi; AND
E) Medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Columvi is not recommended in the following situations:

290. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

915. Columvi™ intravenous infusion [prescribing information]. South San Francisco, CA: Genentech; June 2023.
916. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 10, 2023. Search term: glofitamab.
917. The NCCN B-Cell Lymphoma Clinical Practice Guidelines in Oncology (version 5.2023 – July7, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 10, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Cosela Prior Authorization Policy
- Cosela™ (trilaciclib intravenous infusion – G1 Therapeutics)

REVIEW DATE: 03/22/2023

OVERVIEW

Cosela, a cyclin dependent kinase (CDK) 4/6 kinase inhibitor, is indicated to **decrease the incidence of chemotherapy-induced myelosuppression** when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (SCLC) in adults.[1]

Guidelines

Cosela is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):[2,3]

- **Hematopoietic Growth Factors:** NCCN guidelines (version 2.2023 – March 6, 2023) recommend the use of Cosela as a prophylactic option to decrease the incidence of chemotherapy-induced myelosuppression when administered before (prophylactic granulocyte colony stimulating factor [G-CSF] may be administered after cycle 1) platinum/etoposide ± immune checkpoint inhibitor-containing regimens or a topotecan-containing regimen for extensive-stage SCLC (category 2A). It is also recommended as a prophylactic option to decrease the incidence of anemia and red blood cell transfusions when administered before platinum/etoposide ± immune checkpoint inhibitor-containing regimens or a topotecan-containing regimen for extensive-stage SCLC (category 2B).[2]
- **Small Cell Lung Cancer:** Under supportive care, the NCCN guidelines (version 3.2023 – December 21, 2022) note that Cosela or G-CSF may be used as prophylactic options to decrease the incidence of chemotherapy-induced myelosuppression when administering platinum/etoposide ± immune checkpoint inhibitor-containing regimens or a topotecan-containing regimen for extensive-stage SCLC (category 2A).[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cosela. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cosela as well as the monitoring required for adverse events and long-term efficacy, approval requires Cosela to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cosela is recommended in those who meet the following criteria:

FDA-Approved Indication

66. Small Cell Lung Cancer. Approve for 6 months if the patient meets all of the following criteria (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has extensive-stage disease; AND
- **C)** The medication is used to decrease the incidence of chemotherapy-induced myelosuppression; AND
- **D)** Patient meets ONE of the following criteria (i or ii):
  - **i.** Patient will be receiving a platinum (carboplatin or cisplatin) and etoposide-containing chemotherapy regimen; OR
  - **ii.** Patient will be receiving a topotecan-containing regimen; AND
- **E)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cosela is not recommended in the following situations:

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

18. Cosela™ intravenous infusion [prescribing information]. Durham, NC: G1 Therapeutics, Inc.; February 2021.
19. The NCCN Hematopoietic Growth Factors Clinical Practice Guidelines in Oncology (version 2.2023 – March 6, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 17, 2023.
20. The NCCN Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – December 21, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 17, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Cyramza Prior Authorization Policy
- Cyramza® (ramucirumab intravenous infusion – Eli Lilly)

REVIEW DATE: 06/14/2023

OVERVIEW

Cyramza, a human vascular endothelial growth factor receptor 2 (VEGFR2) antagonist, is indicated for the following:[1]

- **Colorectal cancer**, metastatic, in combination with FOLFIRI (irinotecan, leucovorin, and 5-fluorouracil [5-FU]) for patients with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.
- **Gastric** or **gastroesophageal junction adenocarcinoma**, as a single agent or in combination with paclitaxel for patients with advanced or metastatic disease with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.
- **Hepatocellular carcinoma**, as a single agent in patients who have an alpha fetoprotein of ≥ 400 ng/mL and have been treated with Nexavar® (sorafenib tablets).
- **Non-small cell lung cancer** (NSCLC), metastatic, in combination with docetaxel for patients with disease progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Cyramza.
- **NSCLC**, metastatic, in combination with erlotinib for the first-line treatment of NSCLC with EGFR exon 19 deletions or exon 21 (L858R) mutations.

Guidelines

Cyramza is addressed in National Comprehensive Cancer Network (NCCN) guidelines:

- **Colon Cancer** (version 2.2023 – April 25, 2023) and **rectal cancer** (version 3.2023 – May 26, 2023): Guidelines recommend Cyramza as primary therapy and subsequent therapy for patients with unresectable advanced or metastatic disease, and as adjuvant treatment for unresectable metachronous metastases that converted to resectable disease after primary treatment, in combination with either irinotecan or FOLFIRI.[2-4]
- **Gastric Cancer** (version 1.2023 – March 10, 2023) and **Esophageal and Esophagogastric Junction Cancers** (version 2.2023 – March 10, 2023): Guidelines recommend Cyramza as palliative treatment for patients who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease.[4-6]
- **Hepatobiliary Cancers:** Guidelines (version 1.2023 – March 10, 2023) recommend Cyramza as a single agent for the treatment of progressive disease with an alpha fetoprotein ≥ 400 ng/mL and Child-Pugh Class A only.[4,8]
- **NSCLC:** Guidelines (version 3.2023 – April 13, 2023) recommend Cyramza as subsequent therapy in combination with docetaxel for recurrent, advanced, or metastatic disease for patients who have not previously received docetaxel either following progression on initial cytotoxic therapy or for further progression on a systemic immune checkpoint inhibitor or other systemic therapy.[4,7] Cyramza is also recommended in combination with erlotinib for patients with EGFR exon 19 deletion or exon 21 L858R mutation positive, recurrent, advanced, or metastatic disease as first-line therapy or as continuation therapy following disease progression on Cyramza and erlotinib.

- **Mesothelioma – Pleural:** Guidelines (version 1.2023 – December 15, 2022) recommend Cyramza as subsequent therapy in combination with gemcitabine for pleural mesothelioma, pericardial mesothelioma, and tunica vaginalis testis mesothelioma.[4,9]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cyramza. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cyramza as well as the monitoring required for adverse events and long-term efficacy, approval requires Cyramza to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cyramza is recommended in those who meet one of the following criteria:

FDA-Approved Indications

14. **Colon, Rectal, or Appendiceal Cancer**. Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, D, and E):
    - **A)** Patient is ≥ 18 years of age; AND
    - **B)** Patient has advanced or metastatic disease; AND
    - **C)** Patient has received both of the following (i and ii):
        - **i.** Oxaliplatin; AND
        - **ii.** Fluoropyrimidine (e.g., 5-fluorouracil [5-FU], capecitabine); AND
    - **D)** Cyramza will be used in combination with one of the following (i or ii):
        - **i.** Irinotecan; OR
        - **ii.** FOLFIRI (irinotecan, folinic acid [leucovorin], and 5-fluorouracil [5-FU]); AND
    - **E)** Cyramza is prescribed by or in consultation with an oncologist.

15. **Gastric, Esophagogastric Junction, or Esophageal Cancer**. Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, and D):
    - **A)** Patient is ≥ 18 years of age; AND
    - **B)** Patient meets one of the following criteria (i, ii, or iii):
        - **i.** Cyramza will be used alone; OR
        - **ii.** Cyramza will be used in combination with paclitaxel; OR
        - **iii.** Cyramza will be used in combination with irinotecan; AND
    - **C)** Patient has received chemotherapy with at least ONE of the following (i or ii):
        - **i.** 5-Fluorouracil (5-FU) or capecitabine; OR
        - **ii.** Cisplatin, carboplatin, or oxaliplatin; AND
    - **D)** Cyramza is prescribed by or in consultation with an oncologist.

16. **Hepatocellular Carcinoma.** Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, D, E, and F):
    - **A)** Patient is ≥ 18 years of age; AND
    - **B)** Patient has been treated with Nexavar (sorafenib tablet); AND
    - **C)** Cyramza will be used as a single agent; AND
    - **D)** Patient has an alpha fetoprotein of ≥ 400 ng/mL; AND

E) Patient has Child-Pugh Class A disease; AND
F) Cyramza is prescribed by or in consultation with an oncologist.

17. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets ALL of the following criteria (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patient meets of the following criteria (i or ii):
i. Cyramza will be used as first-line or continuation therapy and the patient meets BOTH of the following (a and b):
a) Patient has epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R mutation positive disease; AND
b) Cyramza will be used in combination with erlotinib; OR
ii. Cyramza will be used as subsequent therapy and the patient meets BOTH of the following (a and b):
a) Cyramza will be used in combination with docetaxel intravenous infusion; AND
b) Patient has received targeted drug therapy if the patient's tumor is positive for a targetable mutation; AND
Note: Examples of targetable mutations include sensitizing epidermal growth factor receptor mutation, anaplastic lymphoma kinase fusions.
C) Cyramza is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

5. Mesothelioma. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has ONE of the following (i, ii, or iii):
i. Pleural mesothelioma; OR
ii. Pericardial mesothelioma; OR
iii. Tunica vaginalis testis mesothelioma; AND
C) Medication is used as subsequent therapy; AND
D) Medication is used in combination with gemcitabine; AND
E) Medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cyramza is not recommended in the following situations:

291. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

446. Cyramza® intravenous infusion [prescribing information]. Indianapolis, IN: Eli Lilly; March 2022.
447. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 6, 2023.
448. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – May 26, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 6, 2023.
449. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 6, 2023. Search term: ramucirumab.
450. The NCCN Gastric Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 6, 2023.

451. The NCCN Esophageal and Esophagogastric Junction Cancers Clinical Practice Guidelines in Oncology (version 2.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 6, 2023.
452. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – April 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 6, 2023.
453. The NCCN HepatocellularCarcinoma Clinical Practice Guidelines in Oncology (version 1.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 6, 2023.
454. The NCCN Mesothelioma Clinical Practice Guidelines in Oncology (version 1.2023 – December 15, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 6, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Danyelza Prior Authorization Policy
- Danyelza® (naxitamab-gqgk intravenous infusion – Y-mAbs Therapeutics)

REVIEW DATE: 12/21/2022

OVERVIEW

Danyelza, a glycolipid disialoganglioside (GD2)-binding monoclonal antibody, is indicated, in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), for the treatment of relapsed or refractory high-risk **neuroblastoma** in the bone or bone marrow in patients ≥ 1 year of age who have demonstrated a partial response, minor response, or stable disease to prior therapy.[1] This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Disease Overview

Neuroblastoma is a rare cancer; however, it is the most common extracranial solid tumor of childhood.[2] Neuroblastoma originates from primodial neural crest cells[3] that develop into sympathetic neural ganglia and adrenal medulla.[2] There are approximately 700 cases diagnosed each year in the US,[4] and around 90% of cases are diagnosed in patients < 5 years of age.[5] Patients most commonly present with an abdominal mass,[4,5] most often arising from the adrenal gland.[2] The mass may be asymptomatic or associated with abdominal pain, hypertension, distension, and constipation. Other tumors may also initiate in the neck, chest, and pelvis.[4] In 10% to 15% of patients, the tumor extends to the epidural or intradural space and may result in spinal cord compression and paraplegia.[2] Patients may also present with proptosis and periorbital ecchymosis, bone pain, pancytopenia, watery diarrhea, presence of Horner syndrome, and subcutaneous skin nodules.[5]

Guidelines

The National Comprehensive Cancer Network has not address Danyelza.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Danyelza. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Danyelza as well as the monitoring required for adverse events and long-term efficacy, approval requires Danyelza to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Danyelza is recommended in those who meet the following criteria:

FDA-Approved Indication

6. Neuroblastoma. Approve for 1 year if the patient meets ALL of the following criteria (A, B, and C):
A) Patient is ≥ 1 year of age; AND
B) Danyelza is used as subsequent therapy; AND
C) Danyelza is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Danyelza is not recommended in the following situations:

292. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

918. Danyelza intravenous infusion [prescribing information]. New York, NY: Y-mAbs Therapeutics; November 2020.
919. Pastor ER, Mousa SA. Current management of neuroblastoma and future direction. *Crit Rev Oncol Hematol*. 2019;138:38-43.
920. Whittle SB, Smith V, Doherty E, et al. Overview and recent advances in the treatment of neuroblastoma. *Expert Rev Anticancer Ther*. 2017;17:369-386.
921. Newman EA, Abdessalam S, Aldrink JH, et al. Update on neuroblastoma. *J Pediatr Surg*. 2019;54:383-389.
922. PDQ® Pediatric Treatment Editoral Board. PDQ Neuroblastoma Treatment. Bethesda, MD: National Cancer Institute. Updated: October 8, 2021. Available at https://www.cancer.gov/types/neuroblastoma/hp/neuroblastoma-treatment-pdq. Accessed on December 3, 2021.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Darzalex Faspro Prior Authorization Policy
- Darzalex Faspro® (daratumumab and hyaluronidase-fihj subcutaneous injection – Janssen)

REVIEW DATE: 06/14/2023

OVERVIEW

Darzalex Faspro, a CD38-directed antibody, is approved for use in adults in the following situations:[1]

- **Light chain amyloidosis**, in newly diagnosed patients, in combination with bortezomib, cyclophosphamide, and dexamethasone. It is a limitation of use that Darzalex Faspro is not indicated and is not recommended in patients with New York Heart Association Class IIIB or Class IV cardiac disease or Mayo Stage IIIB outside of clinical trials.
- **Multiple myeloma**:
  - in newly diagnosed patients, in combination with lenalidomide and dexamethasone, for the treatment of patients who are ineligible for autologous stem cell transplant and in relapsed/refractory disease, in combination with lenalidomide and dexamethasone in patients who have received at least one prior therapy.
  - in newly diagnosed patients, in combination with bortezomib, melphalan, and prednisone in those ineligible for autologous stem cell transplant.
  - in newly diagnosed patients, in combination with bortezomib, Thalomid (thalidomide capsules), and dexamethasone, for treatment of patients who are eligible for autologous stem cell transplant.
  - in patients who have received at least one prior therapy, in combination with bortezomib and dexamethasone.
  - in patients who have received at least one prior therapy (including lenalidomide and a proteasome inhibitor), in combination with Pomalyst (pomalidomide capsules) and dexamethasone.
  - in patients who have received at least three prior lines of therapy (including a proteasome inhibitor and an immunomodulatory agent or who are double-refractory to a proteasome inhibitor and an immunomodulatory agent), as monotherapy.
  - in relapsed/refractory disease, in combination with Kyprolis (carfilzomib intravenous infusion) and dexamethasone in patients who have received one to three prior lines of therapy.

Darzalex Faspro is a fixed combination of daratumumab and hyaluronidase (recombinant human). It contains the identical molecular antibody of daratumumab available in Darzalex intravenous, but hyaluronidase has been added to facilitate systemic delivery. Darzalex Faspro should be administered under the care of a healthcare provider as a 3 to 5 minute subcutaneous injection. The dose of Darzalex Faspro is fixed regardless of the patient's body surface area; dose reductions are not recommended. Safety and efficacy is not established in patients < 18 years of age.

Guidelines

Darzalex Faspro is addressed in guidelines from the National Comprehensive Cancer Network (NCCN).

- **Light Chain Amyloidosis:** The NCCN guidelines (version 2.2023 – November 28, 2022) specifically recommended Darzalex Faspro/bortezomib/cyclophosphamide/dexamethasone as a first-line preferred therapy (category 1) for systemic light chain amyloidosis. Darzalex Faspro or

Darzalex intravenous as monotherapy are among the alternatives for previously treated disease (category 2A).[4]

- **Multiple Myeloma:** The NCCN guidelines (version 3.2023 – December 8, 2022) include Darzalex Faspro in the recommendations for all of the daratumumab-containing regimens. NCCN does recommend Darzalex intravenous or Faspro in multiple regimens both as primary treatment and in previously treated disease. Darzalex/bortezomib/dexamethasone in combination with lenalidomide, Thalomid, or cyclophosphamide and Darzalex/Kyprolis/lenalidomide/dexamethasone are among the regimens recommended as primary therapy for transplant candidates. Darzalex intravenous or Faspro as monotherapy is recommended (category 2A) under "other recommended regimens" as maintenance therapy for transplant candidates. For patients who are non-transplant candidates, Darzalex/lenalidomide/prednisone is a preferred regimen, and Darzalex/bortezomib/melphalan/prednisone and Darzalex/cyclophosphamide/bortezomib/dexamethasone are other recommended regimens for primary treatment. For previously treated multiple myeloma, there are multiple Darzalex-containing regimens in the guidelines, including Darzalex/dexamethasone plus bortezomib, Kyprolis, or lenalidomide (preferred regimens). Darzalex/Pomalyst/dexamethasone is a preferred regimen after two prior therapies, including lenalidomide and a proteasome inhibitor. Darzalex/cyclophosphamide/bortezomib/dexamethasone is an "other recommended regimen", and Darzalex monotherapy (in patients who have received at least three prior therapies) and Xpovio® (selinexor tablets)/Darzalex/dexamethasone are listed as useful in certain circumstances.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Darzalex Faspro. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Darzalex Faspro as well as the monitoring required for adverse events and long-term efficacy, approval requires Darzalex Faspro to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Darzalex Faspro is recommended in those who meet the following criteria:

FDA-Approved Indications

18. Light Chain Amyloidosis. Approve for 1 year if the patient meets all of the following conditions (A, B, C, and D):

a. Patient is ≥ 18 years of age; AND
b. Patient meets ONE of the following (i or ii):
   i. The medication is being used in combination with bortezomib injection, cyclophosphamide, and dexamethasone; OR
   ii. Patient has received at least one other regimen for this condition; AND
   Note: Examples of agents used in other regimens include bortezomib injection, lenalidomide capsules, cyclophosphamide, and melphalan.
c. Patient does NOT have severe heart failure, according to the prescriber; AND
   Note: Severe heart failure is defined as New York Heart Association Class IIIB or IV cardiac disease or Mayo Stage IIIB.
d. The medication is prescribed by or in consultation with an oncologist or a hematologist.

19. Multiple Myeloma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):

20. Patient is ≥ 18 years of age; AND

21. Patient meets ONE of the following (i or ii):

A) The medication is used in combination with at least two other therapies; OR

Note: Examples of medications that may be used in combination with Darzalex Faspro include dexamethasone or prednisone, lenalidomide capsules, Pomalyst (pomalidomide capsules), Thalomid (thalidomide capsules), melphalen, bortezomib, or Kyprolis (carfilzomib intravenous infusion).

B) Patient meets one of the following (a or b):

a) Patient has tried at least three different regimens for multiple myeloma; OR

Note: Examples of agents used in other regimens include bortezomib injection, Kyprolis (carfilzomib injection), lenalidomide capsules, cyclophosphamide, Ninlaro (ixazomib capsules).

b) The medication is used as maintenance therapy in transplant candidates; AND

22. The medication is prescribed by or in consultation with an oncologist or a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Darzalex Faspro is not recommended in the following situations:

293. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

28. Darzalex Faspro [prescribing information]. Horsham, PA: Janssen; November 2022.
29. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 11, 2023. Search term: daratumumab, Darzalex Faspro.
30. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 3.2023 – December 8, 2022). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 11, 2023.
31. The NCCN Systemic Light Chain Amyloidosis Clinical Practice Guidelines in Oncology (version 2.2023 – November 28, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 11, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Darzalex Intravenous Prior Authorization Policy
- Darzalex™ (daratumumab intravenous infusion – Janssen Biotech)

REVIEW DATE: 04/12/2023

OVERVIEW

Darzalex, a CD38-directed cytolytic antibody, is indicated for treatment of **multiple myeloma** in the following situations:[1]

- in newly diagnosed patients, in combination with lenalidomide and dexamethasone, for the treatment of patients who are ineligible for autologous stem cell transplant and in relapsed/refractory disease, in combination with lenalidomide and dexamethasone in patients who have received at least one prior therapy.
- in newly diagnosed patients, in combination with bortezomib, melphalan, and prednisone in those ineligible for autologous stem cell transplant.
- in newly diagnosed patients, in combination with bortezomib, Thalomid (thalidomide capsules), and dexamethasone, for treatment of patients who are eligible for autologous stem cell transplant.
- in patients who have received at least one prior therapy, in combination with bortezomib and dexamethasone.
- in patients who have received at least two prior therapies (including lenalidomide and a proteasome inhibitor), in combination with Pomalyst (pomalidomide capsules) and dexamethasone.
- in patients who have received at least three prior lines of therapy (including a proteasome inhibitor and an immunomodulatory agent or who are double-refractory to a proteasome inhibitor and an immunomodulatory agent), as monotherapy.
- in relapsed/refractory disease, in combination with Kyprolis (carfilzomib intravenous infusion) and dexamethasone in patients who have received one to three prior lines of therapy.

Guidelines

Darzalex Intravenous is discussed in guidelines from the National Comprehensive Cancer Network (NCCN).

- **Multiple Myeloma:** NCCN guidelines (version 3.2023 – December 8, 2022) recommend Darzalex in treatment regimens for primary therapy.[2-3] Darzalex/lenalidomide/bortezomib/dexamethasone, Darzalex/bortezomib/ Thalomid/dexamethasone, Darzalex/Kyprolis/lenalidomide/dexamethasone, and Darzalex/cyclophosphamide/bortezomib/dexamethasone are among the recommended regimens for primary therapy for transplant candidates. For patients who are non-transplant candidates, Darzalex with: lenalidomide/dexamethasone (preferred), and bortezomib/melphalan/prednisone, and cyclophosphamide/bortezomib/dexamethasone are among the regimens for primary treatment. For previously treated multiple myeloma (one to three prior therapies), Darzalex/dexamethasone plus bortezomib, lenalidomide, Pomalyst, or Kyprolis are among the Preferred regimens, whereas other Darzalex-containing regimens are listed as other or useful in certain circumstances. Darzalex has been added under 'Other recommended regimens" for maintenance therapy in transplant candidates.
- **Systemic Light Chain Amyloidosis:** The NCCN guidelines (version 1.2022 June 29, 2021) list Darzalex Intravenous as a therapy for previously treated disease, but not for primary therapy.[4] Of note, Darzalex Faspro is indicated and is specifically recommended as a preferred first-line therapy for systemic light chain amyloidosis, given in combination with cyclophosphamide and dexamethasone.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Darzalex. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Darzalex as well as the monitoring required for adverse events and long-term efficacy, approval requires Darzalex to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Darzalex Intravenous is recommended in those who meet one of the following criteria:

FDA-Approved Indication

20. Multiple Myeloma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **23.** Patient is ≥ 18 years of age; AND
- **24.** Patient meets ONE of the following (i or ii):
  - **A)** Darzalex is used in combination with at least two other therapies; OR
    Note: Examples of therapies that may be used in combination with Darzalex include dexamethasone or prednisone, lenalidomide, Pomalyst (pomalidomide capsules), Thalomid (thalidomide capsules), melphalan, bortezomib, or Kyprolis (carfilzomib intravenous infusion).
  - **B)** Patient meets one of the following (a or b):
    - **a)** Patient has tried at least three different regimens for multiple myeloma; OR
      Note: Examples of agents used in other regimens include bortezomib, Kyprolis, lenalidomide, cyclophosphamide, Ninlaro (ixazomib capsules).
    - **b)** Darzalex is used as maintenance therapy in a transplant candidate; AND
- **25.** The medication is prescribed by or in consultation with an oncologist or a hematologist.

Other Uses with Supportive Evidence

21. Light Chain Amyloidosis. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has received at least one other regimen for this condition.
  Note: Examples of agents used in other regimens include bortezomib, lenalidomide, cyclophosphamide, and melphalan; AND
- **C)** The medication is prescribed by or in consultation with an oncologist or a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Darzalex Intravenous is not recommended in the following situations:

294. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

32. Darzalex [prescribing information]. Horsham, PA: Janssen Biotech; January 2023.
33. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 31, 2023. Search term: daratumumab.

34. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (Version 3.2023 – December 8, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 31, 2023.
35. The NCCN Systemic Light Chain Amyloidosis Clinical Practice Guidelines in Oncology (Version 2.2023 – November 28, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 31, 2023.
36. Kaufman GP, Schrier SL, Lafayette RA, et al. Daratumumab yields rapid and deep hematologic responses in patients with heavily pretreated AL amyloidosis. *Blood*. 2017;130(7):900-902.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Decitabine Products Prior Authorization Policy
- Dacogen® (decitabine intravenous infusion – Otsuka, generic)

REVIEW DATE: 12/13/2023

OVERVIEW

Decitabine (Dacogen), a hypomethylating agent, is indicated for the treatment of **myelodysplastic syndromes** (MDS) in adults including previously treated and untreated, *de novo* and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.[1]

Guidelines

Decitabine is addressed in National Comprehensive Cancer Network (NCCN) guidelines:

- **Acute Myeloid Leukemia:** Guidelines (version 6.2023 – October 24, 2023) recommend decitabine as a single agent, or in combination with Nexavar® (sorafenib tablet) or Venclexta® (venetoclax tablet) for lower intensity therapy and for the treatment of relapsed/refractory disease.[2,4] Decitabine in combination with Venclexta is also recommended for intensive induction therapy. NCCN also recommends decitabine as a single agent for alternative induction therapy in patients < 60 years of age with unfavorable risk genetics with or without TP53 mutation. In addition, decitabine is recommended in combination with Venclexta for relapsed/refractory blastic plasmacytoid dendritic cell neoplasm or as palliative treatment.
- **Myelodysplastic Syndromes:** Guidelines (version 3.2023 – November 10, 2023) recommend decitabine for the treatment of lower risk and higher risk MDS, and for the treatment of myelodysplastic/myeloproliferative neoplasms.[2,3]
- **Myeloproliferative Neoplasms:** Guidelines (version 3.2023 – October 25, 2023) recommend decitabine for the treatment of myelofibrosis (MF)-accelerated phase or MF-blast/acute myeloid leukemia phase.[2,5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of decitabine. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with decitabine as well as the monitoring required for adverse events and long-term efficacy, approval requires decitabine to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of decitabine is recommended in those who meet one of the following criteria:

FDA-Approved Indication

7. **Myelodysplastic Syndromes.** Approve for 1 year if the patient meets the following (A and B):
   Note: Examples include refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia.
   A) Patient is ≥ 18 years of age; AND
   B) The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

8. **Acute Myeloid Leukemia**. Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) The medication is prescribed by or in consultation with an oncologist.

9. **Blastic Plasmacytoid Dendritic Cell Neoplasm**. Approve for 1 year if the patient meets the following (A, B, C, and D):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets one of the following (i or ii):
      i. Patient has relapsed or refractory disease; OR
      ii. Decitabine is used for palliative treatment; AND
   C) Decitabine is used in combination with Venclexta (venetoclax tablet); AND
   D) The medication is prescribed by or in consultation with an oncologist.

10. **Myelofibrosis.** Approve for 1 year if the patient meets the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets ONE of the following (i or ii):
      i. Patient has accelerated phase; OR
      ii. Patient has blast/acute myeloid leukemia phase; AND
   C) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of decitabine is not recommended in the following situations:

295. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

923. Dacogen® intravenous infusion [prescribing information]. Rockville, MD: Otsuka; June 2020.
924. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 8, 2023. Search term: decitabine.
925. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 3.2023 – November 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 8, 2023.
926. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 6.2023 – October 24, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 8, 2023.
927. The NCCN Myeloproliferative Neoplasms Clinical Practice Guidelines in Oncology (version 3.2023 – October 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 8, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Elahere Prior Authorization Policy
- Elahere™ (mirvetuximab soravtansine-gynx intravenous infusion – ImmunoGen)

REVIEW DATE: 11/15/2023

OVERVIEW

Elahere, a folate receptor alpha (FRα)-directed antibody and microtubule inhibitor conjugate, is indicated for the treatment of FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens in adults.[1]

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) ovarian cancer (including fallopian tube cancer and primary peritoneal cancer) clinical practice guidelines (version 2.2023 – June 2, 2023) recommend a variety of treatment options as recurrence therapy for platinum-resistant disease.[2] Single-agent Elahere is listed as a "preferred" targeted therapy for FRα-expressing tumors (category 2A). Other preferred agents include cytotoxic chemotherapy (e.g., oral cyclophosphamide + bevacizumab, docetaxel, etoposide, gemcitabine, or liposomal doxorubicin) [category 2A] and targeted therapy with single-agent bevacizumab (category 2A). Elahere + bevacizumab is listed under "useful in certain circumstances" for FRα-expressing tumors (category 2B).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Elahere. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Elahere as well as the monitoring required for adverse events and long-term efficacy, approval requires Elahere to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Elahere is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Ovarian, Fallopian Tube, or Primary Peritoneal Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   - **26.** Patient is ≥ 18 years of age; AND
   - **27.** Patient has folate receptor alpha positive disease; AND
   - **28.** Patient has platinum-resistant disease; AND
   - **29.** Patient has tried at least one systemic regimen; AND

Note: Examples of a systemic regimen include one or more of the following agents: bevacizumab, cyclophosphamide, docetaxel, etoposide, gemcitabine, paclitaxel, carboplatin, Lynparza (olaparib tablets), or Zejula (niraparib capsules).

30. The medication will be prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Elahere is not recommended in the following situations:

296. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

928. Elahere™ intravenous infusion [prescribing information]. Waltham, MA: ImmunoGen; November 2022.

929. The NCCN Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – June 2, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 10, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Elrexfio Prior Authorization Policy
- Elrexfio™ (elranatamab-bcmm subcutaneous injection – Pfizer)

REVIEW DATE: 08/23/2023

OVERVIEW
Elrexfio, a bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager, is indicated for the treatment of relapsed or refractory **multiple myeloma** in adults who have received at least four prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.[1]

Guidelines
Elrexfio has not been included in the National Comprehensive Cancer Network clinical practice guidelines for multiple myeloma.

Safety
Elrexfio has a Boxed Warning for cytokine release syndrome (CRS) and neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS).[1] In addition, Elrexfio was approved with a Risk Evaluation and Mitigation Strategy (REMS) program due to the risk of CRS and neurologic toxicity, including ICANS.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Elrexfio. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Elrexfio as well as the monitoring required for adverse events and long-term efficacy, approval requires Elrexfio to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Elrexfio is recommended in those who meet the following criteria:

FDA-Approved Indication

11. Multiple Myeloma. Approve for 1 year if the patient meets the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has tried at least four systemic regimens; AND
- **C)** Among the previous regimens tried, the patient has received at least one drug from each of the following classes (i, ii, and iii):
  - **i.** Proteasome inhibitor; AND
    Note: Examples include bortezomib, Kyprolis (carfilzomib intravenous infusion), and Ninlaro (ixazomib capsules).
  - **ii.** Immunomodulatory drug; AND

Note: Examples include lenalidomide, Pomalyst (pomalidomide capsules), and Thalomid (thalidomide capsules).

iii. Anti-CD38 monoclonal antibody; AND
Note: Examples include Darzalex (daratumumab intravenous infusion), Darzalex Faspro (daratumumab and hyaluronidase-fihj subcutaneous injection), and Sarclisa (isatuximab-irfc intravenous infusion).

D) The medication will be prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Elrexfio is not recommended in the following situations:

297. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

930. Elrexfio™ subcutaneous injection [prescribing information]. New York, NY: Pfizer; August 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Elzonris Prior Authorization Policy
- Elzonris™ (tagraxofusp-erzs intravenous infusion – Stemline)

REVIEW DATE: 12/21/2022

OVERVIEW
Elzonris is indicated for the treatment of blastic plasmacytoid dendritic cell neoplasm in patients ≥ 2 years of age.[1]

Elzonris is a CD-123 directed cytotoxin, consisting of recombinant human interleukin-3 (IL-3) fused with truncated diphtheria toxin and is produced by recombinant DNA technology in *Escherichia coli* cells.[1] Elzonris inhibits protein synthesis and causes cell death in cells expressing CD-123.

Guidelines
The National Comprehensive Cancer Network clinical practice guidelines for **acute myeloid leukemia** (version 2.2022 – June 14, 2022) recommend Elzonris as a single agent for the treatment of blastic plasmacytoid dendritic cell neoplasm.[2,3]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Elzonris. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Elzonris as well as the monitoring required for adverse events and long-term efficacy, approval requires Elzonris to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Elzonris is recommended in those who meet the following criteria:

FDA-Approved Indication

12. Blastic Plasmacytoid Dendritic Cell Neoplasm. Approve for 1 year if the patient meets BOTH of the following criteria (A and B):
A) Patient is ≥ 2 years of age; AND
B) Elzonris is prescribed by or consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Elzonris is not recommended in the following situations:

298. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

931. Elzonris™ [prescribing information]. New York, NY: Stemline Therapeutics; November 2022.
932. The NCCN Drugs & Biologics Compendium. © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 19, 2022. Search term: tagraxofusp.
933. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 2.2022 – November 14, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 19, 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Empliciti Prior Authorization Policy
- Empliciti® (elotuzumab intravenous infusion – Bristol-Myers Squibb)

REVIEW DATE: 04/12/2023

OVERVIEW

Empliciti, a SLAMF7 (signaling lymphocytic activation molecule family member 7)-directed immunostimulatory antibody, is indicated in **multiple myeloma**, in the following situations:[1]

- in patients who have received one to three prior therapies, in combination with lenalidomide and dexamethasone.
- in patients who have received at least two prior therapies (including lenalidomide and a proteasome inhibitor), in combination with Pomalyst® (pomalidomide capsules) and dexamethasone.

Guidelines

The National Comprehensive Cancer Network (NCCN) Multiple Myeloma clinical practice guidelines (version 3.2023 – December 8, 2022) recommend Empliciti in treatment regimens for patients who were previously treated for multiple myeloma.[3] In this population, Empliciti/lenalidomide/dexamethasone, Empliciti/bortezomib/dexamethasone and Empliciti/Pomalyst/dexamethasone are listed as among the other recommended regimens.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Emplicti. Because of the specialized skills required for evaluation and diagnosis of patients treated with Emplicti as well as the monitoring required for adverse events and long-term efficacy, approval requires Emplicti to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Empliciti is recommended in those who meet the following criteria:

FDA-Approved Indication

22. Multiple Myeloma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
- **31.** Patient is ≥ 18 years of age; AND
- **32.** Patient has tried at least one other regimen for multiple myeloma; AND
  Note: Examples of agents used in other regimens include bortezomib, lenalidomide, cyclophosphamide, Darzalex (daratumumab intravenous infusion).
- **33.** Empliciti is used in combination with at least one other agent; AND
  Note: Examples of agents that may be used in combination with Empliciti include lenalidomide, bortezomib, and Pomalyst (pomalidomide capsules).
- **34.** Empliciti is prescribed by or in consultation with an oncologist or a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Empliciti is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

37. Empliciti® [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; March 2022.
38. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 9, 2023. Search term: elotuzumab.
39. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (Version 3.2023 – December 8, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 9, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Enhertu Prior Authorization Policy
- Enhertu® (fam-trastuzumab deruxtecan-nxki intravenous infusion – Daiichi Sankyo and AstraZeneca)

REVIEW DATE: 02/22/2023

OVERVIEW

Enhertu is a human epidermal growth factor receptor 2 (HER2)-directed antibody and topoisomerase inhibitor conjugate indicated for the following uses:[1]

- **Breast cancer**
  - Treatment of unresectable or metastatic HER2-positive disease in adults who have received a prior anti-HER2-based regimen either in the metastatic setting or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.
  - Treatment unresectable or metastatic HER2-low (immunohistochemistry [IHC] 1+ or IHC 2+/ in situ hybridization [ISH] negative) breast cancer, as determined by a FDA approved test, in adults who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.
- **Gastric or gastroesophageal junction adenocarcinoma**, treatment of locally advanced or metastatic HER2-positive disease, in adults who have received a prior trastuzumab-based regimen.
- **Non-small cell lung cancer,** treatment of unresectable or metastatic disease in adults whose tumors have an activating HER2 (erb-b2 receptor tyrosine kinase 2 [*ERBB2*]) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.

Enhertu cannot be substituted for or with trastuzumab or Kadcyla® (ado-trastuzumab emtansine intravenous infusion).

Guidelines

Enhertu is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):

- **Breast Cancer:** NCCN guidelines (version 2.2023 – February 7, 2023) recommend Enhertu as a "Preferred" second-line therapy regimen for the treatment of recurrent, unresectable (local or regional), or Stage IV metastatic disease that is HER2-positive (category 1).[2,3] The guidelines note that Enhertu may be considered in the first-line setting as an option for select patients (i.e., those with rapid progression within 6 months of neoadjuvant or adjuvant therapy [12 months for Perjeta® {pertuzumab intravenous infusion}-containing regimens]) [category 2A]. The guidelines recommend Enhertu as a "Preferred" single-agent for recurrent unresectable (local or regional) or stage IV HER2 IHC 1+, or 2+ and ISH negative disease that is HR negative or HR positive with visceral crisis or endocrine therapy refractory (category 1 as second-line; category 2A as later-line therapy). NCCN compendium recommends Enhertu for brain metastases in patients with HER2 positive breast cancer.[2]
- **Colon or Rectal Cancer:** NCCN colon cancer guidelines (version 3.2022 – January 25, 2023) and NCCN rectal cancer guidelines (version 4.2022 – January 25, 2023) recommend Enhertu as primary treatment as a single agent in patients with HER2-amplified and *RAS* and *BRAF* wild-type after previous adjuvant therapy with FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months (category 2A). Enhertu is also recommended as subsequent therapy for HER-2 amplified and *RAS* and *BRAF* wild-type disease (category 2A).[2,4,5]

- **Esophageal and Esophagogastric Junction Cancers**: NCCN guidelines (version 5.2022 – December 5, 2022) recommend Enhertu as a preferred regimen for second-line or subsequent therapy for unresectable locally advanced, recurrent, or metastatic disease (where local therapy is not indicated) for HER2 overexpression positive adenocarcinoma (category 2A).[6]
- **Gastric Cancer:** NCCN guidelines (version 2.2022 – January 11, 2022) recommend Enhertu as a preferred regimen for second-line or subsequent therapy for unresectable locally advanced, recurrent, or metastatic disease (where local therapy is not indicated) for HER2 overexpression positive adenocarcinoma (category 2A).[7] Trastuzumab is recommended as a preferred regimen in addition to first-line chemotherapy (fluorouracil or capecitabine + oxaliplatin [category 2A] or cisplatin [category 1]) in HER2 overexpression positive adenocarcinoma.
- **Non-Small Cell Lung Cancer:** NCCN guidelines (version 2.2023 – February 17, 2023) support use of Enhertu as a preferred single-agent subsequent therapy for *ERBB2* or HER2 mutation positive recurrent, advanced, or metastatic disease.[2,8]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Enhertu. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Enhertu as well as the monitoring required for adverse events and long-term efficacy, approval requires Enhertu to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Enhertu is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Breast Cancer**. Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has recurrent or metastatic breast cancer; AND
   - **C)** Patient meets one of the following criteria (i or ii):
     - **i.** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; OR
     - **ii.** Patient has HER2-low disease as shown by HER2 immunohistochemistry (IHC) 1+, or IHC 2+ and in situ hybridization (ISH) negative disease and meets one of the following criteria (a or b):
       - **a)** Patient has hormone receptor (HR) positive disease and is refractory to endocrine therapy; OR
       - **b)** Patient has HR negative disease; AND
   - **D)** Patient has tried at least one prior regimen; AND
   - **E)** The medication is prescribed by or in consultation with an oncologist.

2. **Gastric or Gastroesophageal Junction Cancer.** Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
   - **C)** Patient has received at least one prior trastuzumab-based regimen; AND

D) The medication is prescribed by or in consultation with an oncologist.

3. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has unresectable or metastatic disease; AND
- **C)** The disease has activating human epidermal growth factor receptor 2 (HER2) mutations; AND
- **D)** Patient has tried at least one prior systemic therapy; AND
- **E)** The medication is prescribed by or in consultation with an oncologist.

B) Other Uses with Supportive Evidence

C)

4. Colon or Rectal Cancer. Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, D, E, and F):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has unresectable, advanced, or metastatic disease; AND
- **C)** Patient has human epidermal growth factor receptor 2 (HER2)-amplified disease; AND
- **D)** Patient has wild-type *RAS* and *BRAF* disease; AND
- **E)** Patient has tried at least one chemotherapy; AND
  - **iii.** Note: Examples of chemotherapy are fluoropyrimidine such as 5-fluorouracil (5-FU), capecitabine; oxaliplatin, irinotecan, or an adjunctive chemotherapy regimen such as FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).
- **F)** The medication is prescribed by or in consultation with an oncologist.

5. Esophageal Cancer. Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **C)** Patient has received at least one prior trastuzumab-based regimen; AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Enhertu is not recommended in the following situations.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

21. Enhertu® intravenous infusion [prescribing information]. Basking Ridge, NJ and Wilmington, DE: Daiichi Sankyo and AstraZeneca; November 2022.
22. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 20, 2023. Search term: fam-trastuzumab deruxtecan-nxki.
23. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – February 7, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 20, 2023.
24. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 3.2022 – January 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 20, 2023.
25. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 4.2022 – January 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 20, 2023.

26. The NCCN Esophageal and Esophagogastric Junction Cancers Clinical Practice Guidelines in Oncology (version 5.2022 – December 5, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 20, 2023.
27. The NCCN Gastric Cancer Clinical Practice Guidelines in Oncology (version 2.2022 – January 11, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 20. 2023.
28. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – February 17, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 20, 2023.

G)

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Epkinly Prior Authorization Policy
- Epkinly™ (epcoritamab-bysp subcutaneous injection – Genmab)

REVIEW DATE: 06/05/2023

OVERVIEW
Epkinly, a bispecific CD20-directed CD3 T-cell engager, is indicated for the treatment of relapsed or refractory **diffuse large B-cell lymphoma** (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma, in adults after two or more lines of systemic therapy.[1]

Guidelines
Epkinly has been addressed by National Comprehensive Cancer Network. The **B-cell lymphoma** clinical practice guidelines (version 4.2023 – June 2, 2023) recommend Epkinly for the third-line and subsequent treatment of DLBCL, histologic transformation of indolent lymphomas to DLBCL, high-grade B-cell lymphomas, human immunodeficiency virus (HIV)-related B-cell lymphomas, and post-transplant lymphoproliferative disorders.[2,3]

Safety
Epkinly has Boxed Warnings for cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome.[1]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Epkinly. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Epkinly as well as the monitoring required for adverse events and long-term efficacy, approval requires Epkinly to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Epkinly is recommended in those who meet the following criteria:

FDA-Approved Indication

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13. Diffuse Large B-Cell Lymphoma: Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
Note: Diffuse large B-cell lymphoma (DLBCL) includes DLBCL not otherwise specified, DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma.
A) Patient is ≥ 18 years of age; AND
B) Patient has received two or more lines of systemic therapy; AND

Note: Examples of systemic therapy include RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and DHA (dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) ± rituximab.

C) Medication is given as a single agent; AND

D) Medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

14. Human Immunodeficiency Virus (HIV)-Related B-Cell Lymphomas. Approve for 1 year if the patient meets the following (A, B, C, and D):

Note: HIV-related B-cell lymphomas includes HIV-related diffuse large B-cell lymphoma (DLBCL), primary effusion lymphoma, and human herpes virus-8 (HHV8) positive DLBCL.

A) Patient is ≥ 18 years of age; AND

B) Patient has received two or more lines of systemic therapy; AND

Note: Examples of systemic therapy include RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin).

C) Medication is given as a single agent; AND

D) Medication is prescribed by or in consultation with an oncologist.

15. Post-Transplant Lymphoproliferative Disorders. Approve for 1 year if the patient meets the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient has received two or more lines of systemic therapy; AND

Note: Examples of systemic therapy include RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine).

C) Medication is given as a single agent; AND

D) Medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Epkinly is not recommended in the following situations:

299. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

934. Epkinly subcutaneous injection [prescribing information]. Plainsboro, NJ: Genmab; May 2023.
935. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 5, 2023. Search term: epcoritamab.
936. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 4.2023 – June 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 5, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Erbitux Prior Authorization Policy
- Erbitux® (cetuximab intravenous infusion – ImClone/Eli Lilly)

REVIEW DATE: 08/02/2023

OVERVIEW

Erbitux, an epidermal growth factor receptor (EGFR) chimeric monoclonal antibody, is indicated for the following uses:[1]

- **Colorectal cancer** (CRC), *KRAS* wild-type, EGFR-expressing, metastatic CRC as determined by an FDA-approved test for the following uses:
  - In combination with FOLFIRI (irinotecan, 5-fluorouracil [5-FU], leucovorin) for first-line treatment.
  - In combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy.
  - As a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.

  Limitation of use: Erbitux is not indicated for treatment of *RAS*-mutant CRC or when the results of the *RAS* mutation tests are unknown.
- **CRC**, metastatic, *BRAF V600E* mutation-positive, as detected by an FDA-approved test, in combination with Braftovi® (encorafenib capsules) for adults after prior therapy.
- **Squamous Cell Carcinoma of the Head and Neck**:
  - In combination with radiation therapy for the initial treatment of locally or regionally advanced disease.
  - In combination with platinum-based therapy with 5-FU for the first-line treatment of patients with recurrent locoregional or metastatic disease.
  - As a single agent in patients with recurrent or metastatic disease for whom prior platinum-based therapy has failed.

Guidelines

Erbitux is addressed in a number of National Comprehensive Cancer Network (NCCN) guidelines:

- **Colon** and **Rectal Cancer:** Guidelines for colon cancer (version 2.2023 – April 25, 2023) recommend Erbitux as primary therapy for unresectable, advanced, or metastatic *KRAS/NRAS/BRAF* wild-type gene and left-sided tumors only, in combination with irinotecan, FOLFOX (5-FU, leucovorin, oxaliplatin), FOLFIRI, or FOLFOXIRI (5-FU, leucovorin, oxaliplatin, irinotecan) regimens in patients who can tolerate intensive therapy or as a single agent in patients who cannot tolerate intensive therapy.[2,6] Reference to left-sided only disease refers to a primary tumor that originated in the left side of the colon. Therapies recommended after first progression vary depending on the initial treatment regimen (i.e., 5-FU/leucovorin-based or capecitabine-based therapy) that was used. The NCCN guidelines recommend Erbitux, in combination with irinotecan, FOLFOX, or FOLFIRI for the subsequent treatment of *KRAS/NRAS/BRAF* wild-type tumors; or in combination with Braftovi for the subsequent treatment of *BRAF V600E* positive disease. The NCCN rectal cancer guidelines (version 3.2023 – May 26, 2023) make the same recommendations for Erbitux for the treatment of rectal cancer.[3,6]
- **Head and Neck Cancer:** Guidelines (version 2.2023 – May 15, 2023) recommend Erbitux in combination with radiation therapy, with a platinum agent (cisplatin or carboplatin) with or without 5-FU, with a platinum agent plus either docetaxel or paclitaxel, or as a single agent.[4,6]

- **Non-Small Cell Lung Cancer:** Guidelines (version 3.2023 – April 13, 2023) recommend Erbitux in combination with Gilotrif® (afatinib tablets) as subsequent therapy for recurrent, advanced, or metastatic disease in patients with a known sensitizing *EGFR* mutation who have progressed on EGFR tyrosine kinase inhibitor (TKI) therapy, and have multiple symptomatic systemic lesions; or with a known sensitizing EGFR mutation who have progressed on EGFR TKI therapy and have asymptomatic disease, symptomatic brain lesions, or isolated symptomatic lesions.[5,6]
- **Penile Cancer:** Guidelines (version 1.2023 – December 1, 2022) recommend Erbitux as a single agent for the subsequent treatment of patients with metastatic disease.[6,7]
- **Squamous Cell Skin Cancer:** Guidelines (version 1.2023 – March 10, 2023) recommend Erbitux as a single agent or in combination with radiation therapy for inoperable or incompletely resected regional disease, or as systemic therapy alone in patients ineligible for checkpoint inhibitors with inoperable or incompletely resected regional disease, or regional recurrence or distant metastases.[6,8]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Erbitux. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Erbitux as well as the monitoring required for adverse events and long-term efficacy, approval requires Erbitux to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Erbitux is recommended in those who meet one of the following criteria:

FDA-Approved Indications

23. Colon and Rectal Cancer. Approve for 1 year if the patient meets the following (A, B, C, D, E, and F):

35. Patient is ≥ 18 years of age; AND

36. Patient has unresectable, advanced, or metastatic disease; AND

37. Patient's tumor or metastases are wild-type *RAS* (*KRAS* wild-type and *NRAS* wild-type) [that is, the tumor or metastases are *KRAS* and *NRAS* mutation negative]; AND

38. The primary tumor originated on the left side of the colon (from splenic flexure to rectum); AND

39. Patient meets ONE of the following (i or ii):

i. Patient's tumor or metastases are wild-type *BRAF* (that is, the tumor or metastases are *BRAF V600E* mutation-negative); OR

ii. Patient's tumor or metastases are *BRAF V600E* mutation-positive and the patient meets BOTH of the following (a and b):

a) Patient has previously received a chemotherapy regimen for colon or rectal cancer; AND
Note: Examples of chemotherapy regimens include a fluoropyrimidine such as 5-fluorouracil (5-FU), capecitabine, oxaliplatin, irinotecan, or an adjunctive chemotherapy regimen such as FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).

b) Erbitux is prescribed in combination with Braftovi (encorafenib capsules); AND

F) Erbitux is prescribed by or in consultation with an oncologist.

24. Head and Neck Squamous Cell Carcinoma. Approve for 1 year if the patient meets the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following (i, ii, iii, or iv):
- **iii.** Erbitux will be used in combination with radiation therapy; OR
- **iv.** Erbitux will be used in combination with platinum-based therapy; OR
  Note: Examples of platinum chemotherapy include cisplatin and carboplatin.
- **v.** Erbitux will be used in combination with Opdivo (nivolumab intravenous infusion); OR
- **vi.** Erbitux will be used as a single agent; AND
- **C)** Erbitux is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

25. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets the following (A, B, C, D, E, and F):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has recurrent, advanced, or metastatic non-small cell lung cancer; AND
- **C)** Patient has a known sensitizing epidermal growth factor receptor *(EGFR)* mutation; AND
  Note: Examples of *EGFR* mutations include *EGFR* exon 19 deletion, or exon 21 *L858R*, or *EGFR S768I*, *L861Q*, and/or *G719X* mutation positive.
- **D)** Patient has received at least ONE tyrosine kinase inhibitor; AND
  Note: Examples of tyrosine kinase inhibitors include erlotinib tablets, Iressa (gefitinib tablets), or Gilotrif (afatinib tablets).
- **E)** Erbitux will be used in combination with Gilotrif (afatinib tablets); AND
- **F)** Erbitux is prescribed by or in consultation with an oncologist.

26. Penile Cancer. Approve for 1 year if the patient meets the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has metastatic disease; AND
- **C)** Erbitux will be used as subsequent therapy; AND
- **D)** Erbitux will be used as a single agent; AND
- **E)** Erbitux is prescribed by or in consultation with an oncologist.

27. Squamous Cell Skin Cancer. Approve for 1 year if the patient meets the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following (i, ii, iii, or iv):
- **i.** Patient has locally advanced, high-risk, or very high-risk disease; OR
- **ii.** Patient has unresectable, inoperable, or incompletely resected regional disease; OR
- **iii.** Patient has local or regional recurrence; OR
- **iv.** Patient has distant metastases; AND
- **C)** Erbitux is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Erbitux is not recommended in the following situations:

300. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

40. Erbitux® intravenous infusion [prescribing information]. Indianapolis, IN: Eli Lilly/ImClone; September, 2021.
41. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 24, 2023.
42. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – May 26, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 24, 2023.
4. The NCCN Head and Neck Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – May 15, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 24, 2023.
5. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – April 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 24, 2023.
6. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 24, 2023. Search term: cetuximab.
7. The NCCN Penile Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – December 1, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 24, 2023.
8. The NCCN Squamous Cell Skin Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 24, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Erwinaze Prior Authorization Policy
- Erwinaze® (asparaginase *Erwinia chrysanthemi* intramuscular or intravenous injection – Jazz)

REVIEW DATE: 05/31/2023

OVERVIEW

Erwinaze, *Erwinia chrysanthemi*-derived L-asparaginase, is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of **acute lymphoblastic leukemia** (ALL) in patients who have developed hypersensitivity to *Escherichia coli*-derived asparaginase.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for **ALL** (version 1.2022 – April 4, 2022) and for **Pediatric ALL** (version 2.2023 – March 10, 2023) recommend *E. chrysanthemi*-derived asparaginase for patients who have systemic allergic reactions or anaphylaxis due to pegaspargase hypersensitivity, and for induction therapy for ALL in patients ≥ 65 years of age.[2-4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Erwinaze. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Erwinaze as well as the monitoring required for adverse events and long-term efficacy, approval requires Erwinaze to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Erwinaze is recommended in those who meet one of the following criteria:

FDA-Approved Indication

16. Acute Lymphoblastic Leukemia. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Erwinaze is used for one of the following (i or ii):
  - **i.** Patient has a systemic allergic reaction or anaphylaxis to a pegylated asparaginase product; OR
  - **ii.** Induction therapy in adults ≥ 65 years of age; AND
- **B)** Erwinaze is prescribed by or consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Erwinaze is not recommended in the following situations.

301. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

937. Erwinaze® intramuscular or intravenous injection [prescribing information]. Palo Alto, CA: Jazz; December 2019.
938. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 1.2022 – April 4, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 11, 2022.
939. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 8, 2023. Search term: asparaginase Erwinia chrysanthemi.
940. The NCCN Pediatric Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 2.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 8, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Fulvestrant Prior Authorization Policy
- Faslodex® (fulvestrant intramuscular injection – AstraZeneca; generic)

REVIEW DATE: 05/24/2023

OVERVIEW

Fulvestrant, an estrogen receptor antagonist, is indicated for breast cancer in the following situations[1]:

- As monotherapy:
  - Hormone receptor-positive (HR+) [i.e., estrogen receptor-positive (ER+) or progesterone receptor-positive (PR+)], human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy.
  - HR+ advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.
- Combination therapy:
  - HR+, HER2-negative advanced or metastatic breast cancer in postmenopausal women, in combination Kisqali® (ribociclib tablets), as initial endocrine based therapy or following disease progression on endocrine therapy.
  - HR+, HER2-negative advanced or metastatic breast cancer, in combination with Ibrance® (palbociclib capsules) or Verzenio® (abemaciclib tablets), in women with disease progression after endocrine therapy.

Fulvestrant binds to the estrogen receptor in a competitive manner.[1] Its affinity to the estrogen receptor is comparable to that of estradiol. By binding to the estrogen receptor, fulvestrant downregulates the estrogen receptor protein in human breast cancer cells.

Guidelines

Fulvestrant is addressed in National Comprehensive Cancer Network (NCCN) guidelines:

- **Breast Cancer:** NCCN guidelines (version 4.2023 – March 23, 2023) recommend fulvestrant as monotherapy and in combination with other agents for the treatment of HR+ breast cancer in postmenopausal women or premenopausal women receiving ovarian ablation or suppression.[2] Fulvestrant is recommended for use as monotherapy or in combination with trastuzumab in women with HR+, HER2-positive breast cancer (category 2A). In women with HR+, HER2-negative breast cancer, fulvestrant is recommended as a first-line, "Preferred" regimen with a CDK4/6 inhibitor (Kisqali, Verzenio) [both category 1]. It is a category 2A regimen for fulvestrant use in combination with Ibrance. Fulvestrant is recommended as one of the "Other Recommended Regimens" in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole). Fulvestrant monotherapy is also recommended as first-and subsequent-line therapy as "Other Recommended Regimens" (category 2A). In these women, fulvestrant is recommended in the second- and subsequent-line setting in combination with CDK4/6 inhibitor (if a CDK4/6 inhibitor was not previously used) [category 1], everolimus (category 2A), or Piqray® (alpelisib tablets) [if the patient has a phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*)-activating mutation] {category 1}. Men with breast cancer should be treated similarly to postmenopausal women, except that the use of an aromatase inhibitor is ineffective without concomitant suppression of testicular steroidogenesis. Fulvestrant with or without Nerlynx® (neratinib tablets) is listed as "Useful in Certain Circumstances" for patients with

estrogen receptor-positive (ER+)/HER2-negative disease who have already received CDK4/6 inhibitor therapy (category 2B).

- **Ovarian Cancer, including Fallopian Tube Cancer and Primary Peritoneal Cancer:** NCCN guidelines (version 1.2023 – December 22, 2022) recommend single-agent fulvestrant as a useful agent for the treatment of low-grade serous carcinoma. (category 2A).[3]
- **Uterine Neoplasms:** NCCN guidelines (version 2.2023 – April 28, 2023) recommend fulvestrant for low grade endometrial carcinoma and for uterine sarcoma (low-grade endometrial stromal sarcoma, adenocarcinoma without sarcomatous overgrowth, or HR+ uterine sarcoma preferably in patient with small tumor volume or an indolent growth pace).[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of fulvestrant. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with fulvestrant, as well as the monitoring required for adverse events and long-term efficacy, approval requires fulvestrant to be prescribed by or in consultation with a physician who specializes in the condition being treated.

In the approval indication, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: men/males are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression. Female/women are defined as individuals with the biological traits of a woman, regardless of the individual's gender identity or gender expression.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of fulvestrant is recommended in those who meet one of the following criteria:

FDA-Approved Indications

28. Breast Cancer – Fulvestrant Monotherapy. Approve for 1 year if the patient meets the following criteria (A, B, and C):

40. Patient has recurrent or metastatic hormone receptor (HR)-positive (i.e., estrogen receptor [ER]- or progesterone receptor [PR]-positive) disease; AND

41. Patient meets one of the following criteria (i or ii):

A) Patient is a postmenopausal female* or a male*; OR

B) Patient is pre/perimenopausal female* and meets one of the following (a or b):

a) Patient is receiving ovarian suppression/ovarian ablation with a gonadotropin-releasing hormone (GnRH) agonist; OR

77. Note: Examples of a GnRH agonist include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), or Zoladex (goserelin acetate subcutaneous implant).

b) Patient has had surgical bilateral oophorectomy or ovarian irradiation; AND

42. The medication is prescribed by or in consultation with an oncologist.

* Refer to the Policy Statement.

29. Breast Cancer – Fulvestrant Combination Therapy. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):

I) Patient has recurrent or metastatic hormone receptor (HR)-positive (i.e., estrogen receptor [ER]- or progesterone receptor [PR]-positive) disease; AND

J) Patient meets ONE of the following criteria (i or ii):

i. Patient is a postmenopausal female* or a male*; OR

ii. Patient is pre/perimenopausal female* and meets one of the following (a or b):

a) Patient is receiving ovarian suppression/ovarian ablation with a gonadotropin-releasing hormone (GnRH) agonist; OR

Note: Examples of a GnRH agonist include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), or Zoladex (goserelin acetate subcutaneous implant).

b) Patient has had surgical bilateral oophorectomy or ovarian irradiation; AND

K) Patient meets one of the following criteria (i or ii):

a. Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer and meets one of the following criteria (a or b):

i. Patient has progressed on or after at least one prior endocrine-based therapy and patient meets one of the following criteria [(1) or (2)]:

Note: Examples of endocrine therapy are tamoxifen, anastrozole, letrozole, exemestane.

1. Patient has a phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha *(PIK3CA)*-mutated tumor and the medication is used in combination with Piqray (alpelisib tablets); OR
2. The medication will be used in combination with everolimus; OR

ii. The medication will be used in combination with a cyclin dependent kinase 4/6 (CDK 4/6) inhibitor or a non-steroidal aromatase inhibitor (i.e., anastrozole or letrozole); OR

Note: Examples of CDK4/6 inhibitors are Kisqali (ribociclib tablets), Ibrance (palbociclib capsules), Verzenio (abemaciclib tablets).

b. Patient has human epidermal growth factor receptor 2 (HER2)-positive breast cancer and the medication is used in combination with a trastuzumab product; AND

L) The medication is prescribed by or in consultation with an oncologist.

* Refer to the Policy Statement.

Other Uses with Supportive Evidence

78.

30. Endometrial Carcinoma. Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

31. Ovarian/Fallopian Tube/Primary Peritoneal Cancer. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient has recurrent low-grade serous carcinoma; AND

B) The medication is prescribed by or in consultation with an oncologist.

79.

32. Uterine Sarcoma. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient meets one of the following criteria (i, ii, or iii):

i. Patient has low-grade endometrial stromal sarcoma; OR

ii. Patient has adenosarcoma without sarcomatous overgrowth; OR

iii. Patient has hormone receptor positive uterinesarcoma; AND

B) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of fulvestrant is not recommended in the following situations:

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

43. Faslodex® intramuscular injection [prescribing information]. Wilmington, DE: AstraZeneca; January 2021.
44. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – March 23, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 22, 2023.
45. The NCCN Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 22, 2023.
46. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (version 2.2023 – April 28, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 22, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Fyarro Prior Authorization Policy
- Fyarro™ (sirolimus protein-bound particles intravenous infusion – Aadi Bioscience)

REVIEW DATE: 01/11/2023

OVERVIEW

Fyarro, a mammalian target of rapamycin (mTOR) inhibitor, is indicated for the treatment of adults with locally advanced unresectable or metastatic **malignant perivascular epithelioid cell tumor (PEComa)**.[1]

In preclinical studies in athymic mice with human tumor xenografts, intravenous administration of Fyarro resulted in higher tumor accumulation of sirolimus, inhibition of an mTOR target in the tumor, and tumor growth inhibition compared with oral sirolimus at the same total weekly dose.

Disease Overview

PEComas are rare mesenchymal tumors composed of histologically and immunohistochemically distinctive perivascular cells.[2,3] Most PEComas are benign; however, malignant PEComa is locally aggressive or metastatic.[2] Malignant PEComa is a type of soft tissue sarcoma with a ≤ 1:1,000,000 annual incidence. The most frequent sites are renal, uterine, and gastrointestinal; more females than males are affected. Some patients with PEComas have responded to mTOR inhibitors (sirolimus, everolimus, or temsirolimus), although these data are limited to case reports and retrospective analyses.

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines address Fyarro:

- **PEComa:** Soft tissue sarcoma guidelines (version 2.2022 – May 17, 2022), recommend Fyarro as the preferred regimen for malignant PEComa in locally advanced unresectable or metastatic disease (category 2A).[3] Other recommended regimens include sirolimus, everolimus, and temsirolimus (category 2A for all). Uterine neoplasm guidelines (version 1.2023 – December 22, 2022) acknowledge Fyarro as useful in certain circumstances for first-line or subsequent therapy in advanced, recurrent/metastatic, or inoperable disease; however, this recommendation only applies to PEComa.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Fyarro. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Fyarro as well as the monitoring required for adverse events and long-term efficacy, approval requires Fyarro to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Fyarro is recommended in those who meet the following criteria:

FDA-Approved Indication

17. Perivascular Epithelioid Cell Tumor (PEComa), Malignant. Approve for 1 year the patient meets the following criteria (A, B, and C):
Note: Examples of possible sites of PEComa include, but are not limited to, the gastrointestinal tract, kidneys, and uterus.
A) Patient is ≥ 18 years of age; AND
B) Patient meets one of the following (i or ii):
i. Patient has locally advanced unresectable disease; OR
ii. Patient has metastatic disease; AND
C) Fyarro is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Fyarro is not recommended in the following situations:

302. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

941. Fyarro™ intravenous infusion [prescribing information]. Pacific Palisades, CA: Aadi Bioscience; November 2021.
942. Wagner AJ, Ravi V, Riedel RF, et al. *nab*-Sirolimus for patients with malignant perivascular epithelioid cell tumors. *J Clin Oncol*. 2021 Nov 20;39(33):3660-3670.
943. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 2.2022 – May 17, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 6, 2023.
944. The NCCN Uterine Neoplasm Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 6, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Gazyva Prior Authorization Policy
- Gazyva® (obinutuzumab intravenous infusion – Genentech)

REVIEW DATE: 12/06/2023

OVERVIEW

Gazyva, a CD20-directed antibody, is indicated for the treatment of:
- **Chronic lymphocytic leukemia**, in combination with chlorambucil in previously untreated patients.
- **Follicular lymphoma**, in combination with bendamustine followed by Gazyva monotherapy, for patients who relapse or are refractory to a rituximab containing regimen.
- **Follicular lymphoma, stage II bulky, III or IV**, in combination with chemotherapy, followed by Gazyva monotherapy for patients achieving at least a partial remission, in previously untreated patients.[1]

Guidelines

Gazyva is addressed in National Comprehensive Cancer Network (NCCN) guidelines:
- **B-cell lymphomas:** Guidelines (version 6.2023 – October 10, 2023) recommend Gazyva for the first-line and second-line treatment of follicular lymphoma (grade 1 or 2) or nodal marginal zone lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CVP (cyclophosphamide, vincristine, and prednisone), or bendamustine; or as single agent maintenance treatment.[2,4] The guidelines also recommend Gazyva as second-line or maintenance therapy for extranodal marginal zone lymphoma of the stomach and extranodal marginal zone lymphoma of nongastric sites, and splenic marginal zone lymphoma. Gazyva is also recommended as a substitute for rituximab products (Rituxan, biosimilars) in patients with intolerance or experiencing rare complications, regardless of histology. Finally, Gazyva is recommended as pretreatment, 7 days prior to the administration of Columvi™ (glofitamab-gxbm intravenous infusion) for the treatment of diffuse large B-cell lymphoma (DLBCL) or histologic transformation of indolent lymphomas to DLBCL.
- **Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL):** Guidelines (version 1.2024 – November 3, 2023) recommend Gazyva for the first-line treatment of CLL/SLL without del(17p)/TP53 mutation in patients < 65 years of age without significant comorbidities, Gazyva is recommended in combination with bendamustine, Calquence® (acalabrutinib capsules), Venclexta® (venetoclax tablets), Imbruvica® (ibrutinib capsules and tablets), high-dose methylprednisolone; or as a single-agent.[2,3] For first-line treatment of CLL/SLL without del(17p)/TP53 mutation in patients ≥ 65 years of age and younger patients with significant comorbidities, Gazyva is recommended in combination with Calquence, Venclexta, high-dose methylprednisolone, chlorambucil, or Imbruvica; or as a single agent. Gazyva is also recommended as a single agent or in combination with Venclexta, Calquence, or high-dose methylprednisolone for the first-line treatment of CLL/SLL with del(17p)/TP53 mutation; as a single agent or in combination with high-dose methylprednisolone for relapsed or refractory CLL/SLL without del(17p)/TP53 mutation; and in combination with Venclexta for retreatment for late relapse after a period of remission in patients with or without del(17p)/TP53 mutations.
- **Hairy Cell Leukemia:** Guidelines (version 1.2024 – November 3, 2023) recommend Gazyva in combination with Zelboraf® (vemurafenib tablets) for initial treatment in patients who cannot tolerate purine analogs including frail patients and those with active infections.[2,5]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Gazyva. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Gazyva as well as the monitoring required for adverse events and long-term efficacy, approval requires Gazyva to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Gazyva is recommended in those who meet one of the following criteria:

FDA-Approved Indications

18. **Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma**. Approve for 6 months if the patient meets the following (A and B):
    A) Patient is ≥ 18 years of age; AND
    B) The medication is prescribed by or in consultation with an oncologist.

19. **Follicular Lymphoma**. Approve for 6 months if the patient meets the following (A, B, and C):
    A) Patient is ≥ 18 years of age; AND
    B) Gazyva is used in ONE of the following situations (i, ii, or iii):
        i. In combination with chemotherapy; OR
        Note: Examples include CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CVP (cyclophosphamide, vincristine, and prednisone), or bendamustine.
        ii. For maintenance treatment following Gazyva in combination with chemotherapy; OR
        iii. Patient experienced an adverse event or intolerance to a rituximab product; AND
        Note: Examples of adverse events or intolerance includes paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, toxic epidermal necrolysis. Examples of rituximab products include Rituxan and biosimilars.
    C) The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

20. **Hairy Cell Leukemia.** Approve for 6 months if the patient meets the following (A, B, C, D, and E):
    A) Patient is ≥ 18 years of age; AND
    B) Patient is unable to tolerate purine analog therapy; AND
    Note: Examples of purine analogs include cladribine and pentostatin.
    C) Gazyva is used as initial therapy; AND
    D) Gazyva is used in combination with Zelboraf (vemurafenib tablets); AND
    E) The medication is prescribed by or in consultation with an oncologist.

21. Marginal Zone Lymphoma. Approve for 6 months if the patient meets the following (A, B, and C):
Note: Includes nodal marginal zone lymphoma, splenic marginal zone lymphoma, extranodal marginal zone lymphoma of the stomach, or extranodal marginal zone lymphoma of nongastric sites (noncutaneous).
A) Patient is ≥ 18 years of age; AND
B) Gazyva is used in ONE of the following situations (i, ii, or iii):
i. First-line therapy for nodal marginal zone lymphoma only; OR
ii. Second-line or subsequent therapy for recurrent or progressive disease; OR
iii. Patient experienced an adverse event or intolerance to a rituximab product: AND
Note: Examples of adverse events or intolerance includes paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, toxic epidermal necrolysis. Examples of rituximab products include Rituxan and biosimilars.
C) The medication is prescribed by or in consultation with an oncologist.

22. Other B-Cell Lymphoma. Approve for 6 months if the patient meets the following (A, B, and C):
Note: Includes diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, histologic transformation of indolent lymphomas to DLBCL, high-grade B-cell lymphoma, Burkitt lymphoma, HIV-related B-cell lymphoma, post-transplant lymphoproliferative disorders, Castleman's disease.
A) Patient is ≥ 18 years of age; AND
B) Patient meets ONE of the following (i or ii):
i. A single dose of Gazyza is used as pretreatment before the first dose of Columvi (glofitamab-gxbm intravenous infusion); OR
ii. Patient experienced an adverse event or intolerance to a rituximab product: AND
Note: Examples of adverse events or intolerance includes paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, toxic epidermal necrolysis. Examples of rituximab products include Rituxan and biosimilars.
C) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Gazyva is not recommended in the following situations:

303. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

945. Gazyva® intravenous infusion [prescribing information]. South San Francisco, CA: Genentech; July 2022.
946. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 27, 2023. Search term: obinutuzumab.
947. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (version 1.2024 – November 3, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 27, 2023.
948. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 6.2023 – October 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 27, 2023.
949. The NCCN Hairy Cell Leukemia Clinical Practice Guidelines in Oncology (version 1.2024 – November 3, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 27, 2023.
950. Columvi™ intravenous infusion [prescribing information]. South San Francisco, CA: Genentech; June 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Gonadotropin-Releasing Hormone Analogs Prior Authorization Policy

- Camcevi™ (leuprolide subcutaneous injection – Accord BioPharma)
- Eligard® (leuprolide acetate subcutaneous injection – Tolmar)
- Firmagon® (degarelix subcutaneous injection – Ferring)
- Trelstar® (triptorelin pamoate intramuscular injection – Verity)
- Leuprolide Depot (leuprolide acetate 22.5 mg for depot suspension [formerly Lutrate Depot] – Cipla USA, Inc.)

REVIEW DATE: 01/11/2023; selected revision 04/26/2023

OVERVIEW

Camcevi, Eligard, Leuprolide Depot (formerly Lutrate Depot), Firmagon, and Trelstar are all indicated for the treatment of advanced **prostate cancer**.[1-4,8] Camcevi, Eligard, Leuprolide Depot, and Trelstar are gonadotropin-releasing hormone (GnRH) agonists, whereas Firmagon is a GnRH antagonist.

Guidelines

The GnRH analogs have been addressed in National Comprehensive Cancer Network (NCCN) guidelines:

- **Head and Neck Cancer:** NCCN guidelines (version 1.2023 – December 20, 2022) recommend androgen receptor therapy (e.g., leuprolide and bicalutamide) for patients with recurrent, unresectable, or metastatic androgen receptor positive salivary gland tumors.[5,6]
- **Prostate Cancer:** NCCN guidelines (version 1.2023 – September 16, 2022) note androgen deprivation therapy as primary systemic therapy for regional or advanced disease and as neoadjuvant/concomitant/adjuvant therapy in combination with radiation in localized or locally advanced prostate cancers. Many drugs can be used as androgen deprivation therapy, including Camcevi, Eligard, Firmagon, and Trelstar.[7]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Camcevi, Eligard, Leuprolide Depot, Firmagon, and Trelstar. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Camcevi, Eligard, Leuprolide Depot, Firmagon, and Trelstar as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Camcevi, Eligard, Leuprolide Depot, Firmagon, or Trelstar is recommended in those who meet one of the following criteria:

FDA-Approved Indication

23. Prostate Cancer. Approve Camcevi, Eligard, Leuprolide Depot, Firmagon, or Trelstar for 1 year if prescribed by or in consultation with an oncologist or urologist.

Other Uses with Supportive Evidence

24. Head and Neck Cancer – Salivary Gland Tumors. Approve Camcevi or Eligard for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient has recurrent, unresectable, or metastatic disease; AND
- **B)** Patient has androgen receptor-positive disease; AND
- **C)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Camcevi, Eligard, Leuprolide Depot, Trelstar, or Firmagon is not recommended in the following situations:

304. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

951. Eligard® subcutaneous injection [prescribing information]. Fort Collins, CO: Tolmar; April 2019.
952. Firmagon® subcutaneous injection [prescribing information]. Parsippany, NJ: Ferring; February 2020.
953. Trelstar® intramuscular injection [prescribing information]. Wayne, PA: Verity; May 2020.
954. Camcevi subcutaneous injection [prescribing information]. Durham, NC: Accord BioPharma; May 2021.
955. The NCCN Head and Neck Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – December 20, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 9, 2023.
956. The NCCN Drugs and Biologics Compendium. © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 9, 2023. Search terms: leuprolide acetate, degarelix, triptorelin pamoate.
957. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – September 16, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 9, 2023.
958. Lutrate Depot intramuscular injection [prescribing information]. Warren, NJ: Cipla USA, Inc; February 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Halaven Prior Authorization Policy
- Halaven® (eribulin mesylate intravenous infusion– Eisai)

REVIEW DATE: 03/22/2023

OVERVIEW

3. Halaven, a microtubule inhibitor, is indicated for the following uses:[1]
- **Breast cancer**, metastatic, in patients who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.
- **Liposarcoma,** for the treatment of patients with unresectable or metastatic disease who have received a prior anthracycline-containing regimen.

Guidelines

Halaven has been addressed in National Comprehensive Cancer Network (NCCN) guidelines:[2-5]
- **Breast Cancer:** Guidelines (version 3.2023 – March 3, 2023) list Halaven as one of the preferred single-agent regimens for patients with human epidermal growth factor receptor-2 (HER2)-negative recurrent or metastatic breast cancer.[2] Halaven, in combination with trastuzumab or Margenza® (margetuximab-cmkb intravenous infusion) is also recommended (fourth line and beyond) for the treatment of recurrent or metastatic HER2-positive disease. Both of these are category 2A recommendations.
- **Soft Tissue Sarcoma:** Guidelines (version 2.2022 – May 17, 2022) list Halaven as a subsequent line of treatment of advanced or metastatic soft tissue sarcoma.[3] Halaven is a category 1 recommendation for liposarcoma and category 2A for other subtypes. The NCCN compendium recommends Halaven for the following soft tissue sarcoma subtypes: extremity/body wall, head/neck, retroperitoneal/intra-abdominal, solitary fibrous tumor, and pleomorphic rhabdomyosarcoma.[4]
- **Uterine Neoplasms:** Guidelines (version 1.2023 – December 22, 2022) list Halaven under "other recommended regimens" as second-line or subsequent therapy for the treatment of patients with recurrent or metastatic uterine sarcoma (category 2B).[5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Halaven. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Halaven as well as the monitoring required for adverse events and long-term efficacy, approval requires Halaven to be prescribed by or in consultation with a prescriber who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Halaven is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Breast Cancer.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has recurrent or metastatic disease; AND
   - **C)** Patient meets one of the following (i, ii, or iii):
     - **i.** Patient has human epidermal growth factor receptor 2 (HER2)-negative and hormone-receptor (HR)-positive disease and meets one of the following (a, b, or c):
       - **a)** The medication will be used in the first-line setting and the tumor has no germline *BRCA* mutation; OR
       - **b)** The medication will be used second-line because the patient is not a candidate for Enhertu (fam-trastuzumab deruxtecan-nxki intravenous infusion) therapy; OR
       - **c)** The medication will be used after at least two prior chemotherapy regimens; OR
         PPPP) Note: Examples of chemotherapy regimens include doxorubicin, epirubicin, paclitaxel, docetaxel, Abraxane (albumin-bound paclitaxel intravenous infusion).
     - **ii.** Patient has triple-negative breast cancer and meets one of the following (a or b):
       - **a)** The medication will be used in the first-line setting if the programmed death ligand-1 (PD-L1) combined positive score (CPS) < 10 and there is no germline *BRCA* mutation; OR
       - **b)** The medication is used as subsequent therapy (second-line or beyond); OR
     - **iii.** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease and meets both of the following (a and b):
       - **a)** The medication will be used in fourth-line therapy or beyond; AND
       - **b)** The medication will be used in combination with Margenza (margetuximab-cmkb intravenous infusion) or trastuzumab; AND
   - **D)** The medication is prescribed by or in consultation with an oncologist.

2. **Soft Tissue Sarcoma.** Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has unresectable, progressive, or advanced/metastatic disease; AND
   - **C)** Patient has been treated with at least one prior anthracycline-containing chemotherapy regimen; AND
     Note: Examples of chemotherapy regimens include doxorubicin and dacarbazine, doxorubicin with ifosfamide and mesna, epirubicin with ifosfamide and mesna.
   - **D)** Patient has ONE of the following subtypes (i, ii, iii, iv, or v):
     - **i.** Liposarcoma; OR
     - **ii.** Pleomorphic rhabdomyosarcoma; OR
     - **iii.** Retroperitoneal/intra-abdominal soft tissue sarcoma; OR
     - **iv.** Soft tissue sarcoma of the extremity/body wall; OR
     - **v.** Soft tissue sarcoma of the head/neck; AND
   - **E)** The medication is prescribed by or in consultation with an oncologist.

4.

Other Uses with Supportive Evidence

5. **Uterine Sarcoma.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has recurrent or metastatic disease; AND

C) Patient has been treated with at least one prior chemotherapy regimen; AND

QQQQ) Note: Examples of chemotherapy regimens include doxorubicin, docetaxel, gemcitabine, ifosfamide, dacarbazine, epirubicin.

D) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Halaven is not recommended in the following situations:

140. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

266. Halaven® intravenous infusion [prescribing information]. Nutley, NJ: Eisai; September 2022.
267. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – March 3, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 9, 2023.
268. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 2.2022 – May 17, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 10, 2023.
269. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 10, 2023. Search term: eribulin mesylate.
270. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 10, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Herceptin Hylecta Prior Authorization Policy
- Herceptin Hylecta™ (trastuzumab and hyaluronidase-oysk subcutaneous injection – Genentech)

REVIEW DATE: 03/22/2023

OVERVIEW

Herceptin Hylecta is indicated for the following uses:[1]

- **Breast Cancer, adjuvant treatment** of adults with human epidermal growth factor receptor 2 (HER2) overexpressing node positive or node negative (estrogen receptor [ER]-/progesterone receptor [PR]-negative or with one high risk feature) breast cancer:
  - **a)** As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel.
  - **b)** As part of a treatment regimen with docetaxel and carboplatin.
  - **c)** As a single agent following multi-modality anthracycline based therapy.
- **Breast Cancer**, metastatic, in adults with HER2-overexpressing disease:
  - **a)** In combination with paclitaxel for first-line treatment.
  - **b)** As a single agent for the treatment of patients who have received one or more chemotherapy regimens for metastatic disease.

Guidelines

The National Comprehensive Cancer Network (NCCN) breast cancer clinical practice guidelines (version 3.2023 – March 3, 2023) state that Herceptin Hylecta may be substituted for trastuzumab intravenous and used as a single-agent or in combination with other systemic therapies.[2,3] The guidelines note the different dose and dosage form of Herceptin Hylecta compared with trastuzumab. It is also noted that Herceptin Hylecta cannot be substituted for Kadcyla® (ado-trastuzumab emtansine intravenous infusion) or Enhertu® (fam-trastuzumab deruxtecan-nxki intravenous infusion). Trastuzumab is recommended as part of a preferred regimen in the preoperative, adjuvant, and metastatic setting for HER2-positive disease.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Herceptin Hylecta. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Herceptin Hylecta as well as the monitoring required for adverse events and long-term efficacy, approval requires Herceptin Hylecta to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Herceptin Hylecta is recommended in those who meet the following criteria:

FDA-Approved Indication

67. Breast Cancer. Approve for the duration noted below if the patient meets ALL of the criteria (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND
B) Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
C) Patient meets one of the following criteria (i or ii):
  i. Approve for up to 1 year (total) if the medication is used for adjuvant treatment; OR
  ii. Approve for 1 year if the medication is used for recurrent or metastatic disease; AND
D) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Herceptin Hylecta is not recommended in the following situations:

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

29. Herceptin Hylecta™ subcutaneous injection [prescribing information]. South San Francisco, CA: Genentech; February 2019.
30. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – March 3, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 13, 2023.
31. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 10, 2023. Search term: Herceptin Hylecta.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Imjudo Prior Authorization Policy
- Imjudo® (tremelimumab-actl intravenous infusion – AstraZeneca)

REVIEW DATE: 10/25/2023

OVERVIEW

Imjudo, a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) monoclonal antibody is indicated for the following uses:[1]

- **Hepatocellular carcinoma**, in combination with Imfinzi® (durvalumab intravenous infusion), for the treatment of adults with unresectable disease.
- **Non-small cell lung cancer** (NSCLC), in combination with Imfinzi and platinum-based chemotherapy, for the treatment of adults with metastatic disease and no epidermal growth factor receptor (*EGFR*) mutations or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations.

Guidelines

Imjudo is addressed in the National Comprehensive Cancer Network guidelines.

- **Esophageal and Esophagogastric Junction Cancers:** The guidelines (version 3.2023 – August 29, 2023) recommend Imjudo in combination with Imfinzi for the neoadjuvant treatment of microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) adenocarcinoma in patients who are medically fit for surgery.[2,5]
- **Gastric Cancer:** The guidelines (version 2.2023 – August 29, 2023) recommend Imjudo in combination with Imfinzi for the neoadjuvant treatment of microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) locoregional disease in patients who are medically fit for surgery.[2,6]
- **Hepatocellular Carcinoma:** The guidelines (version 2.2023 – September 14, 2023) recommend Imjudo as a preferred first-line treatment in combination with Imfinzi for unresectable or metastatic hepatocellular carcinoma, or in patients who are not surgical candidates.[2,3]
- **Non-Small Cell Lung Cancer:** The guidelines (version 4.2023 – October 18, 2023) recommend Imjudo, in combination with Imfinzi, plus chemotherapy for the first-line treatment of recurrent, advanced, or metastatic disease with programmed death-ligand 1 (PD-L1) expression ≥ 1% and negative for actionable molecular markers.[2,4] The guidelines also recommend Imjudo in combination with Imfinzi plus chemotherapy for disease with PD-L1 expression < 1%, and for disease that is positive for a variety of molecular markers.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Imjudo. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Imjudo as well as the monitoring required for adverse events and long-term efficacy, approval requires Imjudo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Imjudo is recommended in those who meet one of the following criteria:

FDA-Approved Indications

25. Hepatocellular Carcinoma. Approve for 30 days if the patient meets ALL of the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following (i or ii):
  - **i.** Patient has unresectable or metastatic disease; OR
  - **ii.** According to the prescriber, the patient is not a surgical candidate; AND
- **C)** Imjudo is used as first-line systemic therapy; AND
- **D)** Imjudo is used in combination with Imfinzi (durvalumab intravenous infusion); AND
- **E)** The medication is prescribed by or in consultation with an oncologist.

26. Non-Small Cell Lung Cancer. Approve for 6 months if the patient meets ALL of the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has recurrent, advanced, or metastatic disease; AND
- **C)** Imjudo is used in combination with Imfinzi (durvalumab intravenous infusion); AND
- **D)** Patient meets ONE of the following (i, ii, iii, or iv):
  - **i.** Patient meets BOTH of the following (a and b):
    - **a)** The tumor is negative for actionable molecular markers; AND
      Note: Examples of actionable molecular markers include epidermal growth factor receptor (*EGFR*) mutations, anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations, *KRAS*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET*, *RET*, and *ERBB2* (*HER2*).
    - **b)** Imjudo is used as first-line therapy; OR
  - **ii.** Patient meets both of the following (a and b):
    - **a)** The tumor is positive for ONE of the following [(1), (2), or (3)]:
      - **(1)** Epidermal growth factor receptor (*EGFR*) exon 20 mutation positive; OR
      - **(2)** *KRAS G12C* mutation positive; OR
      - **(3)** *ERBB2* (*HER2*) mutation positive; AND
    - **b)** Imjudo is used as first-line therapy; OR
  - **iii.** Patient meets BOTH of the following (a and b):
    - **a)** The tumor is positive for ONE of the following [(1), (2), (3), or (4)]:
      - **(1)** *BRAF V600E* mutation positive; OR
      - **(2)** *NTRK1/2/3* gene fusion positive; OR
      - **(3)** *MET* exon 14 skipping mutation positive; OR
      - **(4)** *RET* rearrangement positive; AND
    - **b)** Imjudo is used as first-line or subsequent therapy; OR
  - **iv.** Patient meets ALL of the following (a, b, and c):
    - **a)** The tumor is positive for ONE of the following [(1), (2), (3), or (4)]:
      - **(1)** *EGFR* exon 19 deletion or exon 21 L858R mutation positive; OR
      - **(2)** *EGFR S768I*, *L861Q*, and/or *G719X* mutation positive; OR
      - **(3)** *ALK* rearrangement positive; OR
      - **(4)** *ROS1* rearrangement; AND
    - **b)** The patient has received targeted drug therapy for the specific mutation; AND
      Note: Examples of targeted drug therapy include Gilotrif (afatinib tablets), Tagrisso (osimertinib tablets), erlotinib, Iressa (gefitinib tablets), Xalkori (crizotinib capsules), Zykadia (ceritinib capsules), Alecensa (alectinib capsules), Alunbrig (brigatinib tablets),

Lorbrena (lorlatinib tablets), Rozlytrek (entrectinib capsules), or Vizimpro (dacomitinib tablets).

c) Imjudo is used as subsequent therapy; AND

E) The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

27. Esophageal and Esophagogastric Junction Cancers. Approve for 30 days if the patient meets ALL of the following (A, B, C, D, E, F, and G):

A) Patient is ≥ 18 years of age; AND

B) Patient has adenocarcinoma tumor; AND

C) Patient has microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) disease; AND

D) Imjudo is as neoadjuvant therapy; AND

E) Imjudo is used in combination with Imfinzi (durvalumab intravenous infusion); AND

F) According to the physician, the patient is medically fit for surgery; AND

G) The medication is prescribed by or in consultation with an oncologist.

28. Gastric Cancer. Approve for 3o days if the patient meets ALL of the following (A, B, C, D, E, F, and G):

A) Patient is ≥ 18 years of age; AND

B) Patient has locoregional disease; AND

C) Patient has microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) disease; AND

D) Imjudo is as neoadjuvant therapy; AND

E) Imjudo is used in combination with Imfinzi (durvalumab intravenous infusion); AND

F) According to the physician, the patient is medically fit for surgery; AND

G) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Imjudo is not recommended in the following situations:

305. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

959. Imjudo® intravenous infusion [prescribing information]. Wilmington, DE: AstraZeneca; November 2022.
960. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 20, 2023. Search term: tremelimumab.
961. The NCCN Hepatocellular Carcinoma Clinical Practice Guidelines in Oncology (version 2.2023 – September 14, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed October 20, 2023.
962. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – October 18, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed October 20, 2023.
963. The NCCN Esophageal and Esophagogastric Junction Cancers Clinical Practice Guidelines in Oncology (version 3.2023 – August 29, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed October 20, 2023.
964. The NCCN Gastric Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – August 29, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed October 20, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Imlygic Prior Authorization Policy
- Imlygic® (talimogene laherparepvec intralesional injection – Amgen)

REVIEW DATE: 04/05/2023

OVERVIEW

Imlygic is an oncolytic viral therapy indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with **melanoma** recurrent after initial surgery.[1] Limitation of use: Imlygic has not been shown to improve overall survival or have an effect on visceral metastases. Safety and efficacy have not been established in patients < 18 years of age.

Dosing

In the pivotal trial, the initial dose of Imlygic was administered at 10^6 plaque forming units (PFU)/mL (to seroconvert herpes simplex virus-seronegative patients). Subsequent doses were 10^8 PFU/mL administered 3 weeks after the first dose, then every 2 weeks. Total volume of Imlygic was up to 4.0 mL per treatment session. It may not be possible to inject all lesions at each treatment visit or over the full course of treatment. Previously injected and/or uninjected lesions may be injected at subsequent treatment visits. Continue treatment for at least 6 months unless other treatment is required or until there are no injectable lesions to treat. Imlygic may be reinitiated if new unresectable cutaneous, subcutaneous, or nodal lesions appear after a complete response.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for melanoma (version 2.2023 – March 10, 2023) list Imlygic as an option in multiple treatment situations, including for Stage III melanoma; for recurrent disease (including nodal recurrence); for disseminated metastatic disease; and in combination with Yervoy (ipilimumab intravenous infion), for metastatic or unresectable disease following disease progression or maximal clinical benefit from BRAF targeted therapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Imlygic. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Imlygic as well as the monitoring required for adverse events and long-term efficacy, approval requires Imlygic to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indication

G) Melanoma. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy (This includes reinitiation in patients with new lesions following a complete response). Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Imlygic will be directly injected into advanced, metastatic, recurrent, or unresectable cutaneous, subcutaneous, or nodal lesions; AND

iii. Imlygic will be administered by or under the supervision of an oncologist, dermatologist, or surgeon.

B) Patient is Currently Receiving Imlygic. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has remaining injectable lesions for treatment; AND

ii. According to the prescriber, the patient has not experienced clinically relevant disease progression (e.g., disease progression associated with a decline in performance status and/or alternative therapy was needed); AND

iii. Imlygic will be administered by or under the supervision of an oncologist, dermatologist, or surgeon.

80.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Imlygic is not recommended in the following situations:

81.

1. **Concurrent Use with Anti-Herpetic Viral Agents.** Imlygic is a genetically modified, live, attenuated herpes simplex virus-1 that is sensitive to acyclovir. Anti-herpetic viral agents (e.g., acyclovir, valacyclovir, famciclovir) may interfere with efficacy.

2. **Immunocompromised Patients.** Imlygic is contraindicated in patients who are immunocompromised, including those with a of primary or acquired immunodeficient states, leukemia, lymphoma, acquired immunodeficiency syndrome, or other clinical manifestations of infection with human immunodeficiency viruses, and those on immunosuppressive therapy.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

82.

REFERENCES

1. Imlygic intralesional injection [prescribing information]. Thousand Oaks, CA: BioVex/Amgen; February 2023.
2. Dharmadhikari N, Mehnert JM, Kaufman HL. Oncolytic virus immunotherapy for melanoma. *Curr Treat Options Oncol.* 2015;16(3):326.
3. Moehler M, Goepfert K, Heinrich B, et al. Oncolytic virotherapy as emerging immunotherapeutic modality: potential of parvovirus h-1. *Front Oncol.* 2014;4:92.
4. The NCCN Cutaneous Melanoma Clinical Practice Guidelines in Oncology (version 2.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 2, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Ixempra Prior Authorization Policy
- Ixempra® (ixabepilone intravenous infusion – R-Pharm US)

REVIEW DATE: 12/20/2023

OVERVIEW

Ixempra, a microtubule inhibitor, is indicated in combination with capecitabine for the treatment of patients with metastatic or locally advanced **breast cancer** resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated.[1] Ixempra is indicated as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine.

Anthracycline resistance is defined as progression while on therapy or within 6 months in the adjuvant setting or 3 months in the metastatic setting.[1] Taxane resistance is defined as progression while on therapy or within 12 months in the adjuvant setting or 4 months in the metastatic setting.

Guidelines

The National Comprehensive Cancer Network (NCCN) **breast cancer** (version 5.2023 – December 5, 2023) clinical practice guidelines and Compendium recommend Ixempra as a single agent for invasive recurrent unresectable locoregional or invasive stage IV human epidermal growth factor receptor 2 (HER2)-negative disease and in combination with trastuzumab for HER2-positive disease.[2,3] Ixempra is recommended for inflammatory disease as a single agent for patients with no response to preoperative systemic therapy, or recurrent unresectable locoregional or stage IV HER2-negative disease and in combination with trastuzumab for HER2-positive disease.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ixempra. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ixempra as well as the monitoring required for adverse events and long-term efficacy, approval requires Ixempra to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ixempra is recommended in those who meet the following criteria:

FDA-Approved Indication

29. Breast Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following (i, ii, or iii):
  - **i.** Patient has recurrent unresectable local or regional disease; OR
  - **ii.** Patient has metastatic disease; OR
  - **iii.** Patient has no response to preoperative systemic therapy; AND
- **C)** Ixempra is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ixempra is not recommended in the following situations:

306. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

965. Ixempra® intravenous infusion [prescribing information]. Princeton, NJ: R-Pharm US; January 2023.
966. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 18, 2023. Search term: ixabepilone.
967. The NCCN Breast Cancer Clinical Practice Guidelines (version 5.2023 – December 5, 2023). © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 18, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Jevtana Prior Authorization Policy
- Jevtana® (cabazitaxel intravenous infusion – Sanofi-Aventis)

REVIEW DATE: 03/08/2023

OVERVIEW
- Jevtana, a microtubule inhibitor, is indicated in combination with prednisone for the treatment of patients with **metastatic castration-resistant prostate cancer (CRPC)** previously treated with a docetaxel-containing treatment regimen.[1]
-

Guidelines

The National Comprehensive Cancer Network (NCCN) prostate cancer guidelines (version 1.2023 – September 16, 2022) list Jevtana, in combination with a steroid, as a "Preferred" regimen for patients who have received prior docetaxel and novel hormone therapy without visceral metastases (category 1), or with visceral metastases (category 2B).[2,3] Jevtana in combination with a steroid is a "Preferred" regimen for patients who have received prior docetaxel without prior novel hormone therapy (category 2A). The guidelines note that Jevtana (in combination with steroid) can also be considered in patients who are not candidates for docetaxel or are intolerant to docetaxel (category 2A). Jevtana in combination with carboplatin is "Useful in Certain Circumstances" in patients who have received prior docetaxel and/or novel hormone therapy. In addition, Jevtana in combination with carboplatin and a steroid (category 2A) is recommended for the treatment of small cell/neuroendocrine prostate cancer in fit patients with aggressive variant prostate cancer or in patients with unfavorable genomics defined as having defects in at least two of the following: phosphatase and tensin homolog (*PTEN*), tumor protein p53 (*TP53*), and retinoblastoma transcriptional corepressor 1 (*RB1*).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Jevtana. Because of the specialized skills required for evaluation and diagnosis of patients treated with Jevtana as well as the monitoring required for adverse events and long-term efficacy, approval requires the medication to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Jevtana is recommended in those who meet the following criteria:

FDA-Approved Indication

2. **Prostate Cancer.** Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, and D):
   - **A)** Patient has metastatic castration-resistant prostate cancer; AND
   - **B)** The medication will be used in combination with a systemic corticosteroid (e.g., prednisone); AND
   - **C)** Patient meets one of the following criteria (i, ii, iii, or iv):

i. Patient has small cell/neuroendocrine prostate cancer and meets one of the following criteria (a or b):
  a) According to the prescriber, the patient is fit and has aggressive variant disease; OR
  b) Patient has unfavorable genomics with defects in at least two of the following: phosphatase and tensin homolog (*PTEN*), tumor protein p53 (*TP53*), and retinoblastoma transcriptional corepressor 1 (*RB1*); OR

ii. Patient has been previously treated with a docetaxel-containing treatment regimen; OR

iii. Patient is not a candidate or is intolerant to docetaxel therapy, according to the prescriber; OR

iv. Patient has been treated with novel hormone therapy; AND
- Note: Examples of novel hormone therapy include abiraterone, Erleada (apalutamide tablet), Nubeqa (darolutamide tablet), and Xtandi (enzalutamide tablet and capsule).

D) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Jevtana is not recommended in the following situations:

141. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

271. Jevtana® intravenous infusion [prescribing information]. Bridgewater, NJ: Sanofi-Aventis; February 2021.
272. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 28, 2023. Search term: cabazitaxel.
273. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – September 16, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 28, 2023.

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PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Kadcyla Prior Authorization Policy
- Kadcyla® (ado-trastuzumab emtansine intravenous infusion – Genentech)

REVIEW DATE: 08/30/2023

OVERVIEW

Kadcyla, a human epidermal growth factor receptor 2 (HER2)-targeted antibody and microtubule inhibitor conjugate, is indicated for the treatment of patients with HER2-positive breast cancer as a single agent for the following uses:[1]

- **Early breast cancer**, for the adjuvant treatment in patients who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.
- **Metastatic breast cancer**, in patients who previously received trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy.

Guidelines

Kadcyla is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):

- **Breast Cancer:** NCCN guidelines (version 4.2023 – March 23, 2023) recommend Kadcyla as a preferred adjuvant therapy in patients who have residual disease after receiving neoadjuvant (preoperative) therapy (category 1).[2-3] Kadcyla is also recommended for the treatment of HER2-positive recurrent unresectable (local or regional) or Stage IV metastatic disease as a preferred second line regimen (category 2A).[2-3]
- **Head and Neck Cancers:** NCCN guidelines (version 2.2023 – May 15, 2023) recommend Kadcyla as a systemic therapy option for recurrent, unresectable, or metastatic salivary gland tumors (useful in certain circumstances) for HER2 positive tumors (category 2A).[3,4]
- **Non-Small Cell Lung Cancer:** NCCN guidelines (version 3.2023 – April 13, 2023) recommend Kadcyla for erb-b2 receptor tyrosine kinase 2 (ERBB2) or HER2 mutations NSCLC (category 2A).[3,5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Kadcyla. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kadcyla, as well as the monitoring required for adverse events and long-term efficacy, approval requires Kadcyla to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kadcyla is recommended in those who meet one of the following criteria:

FDA-Approved Indication

68. Breast Cancer. Approve if the patient meets the following (A, B, C, and D):
- **H)** Patient is ≥ 18 years of age; AND
- **I)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **J)** Patient meets ONE of the following (i or ii):
  - **83. i.** Approve for 1 year if Kadcyla is used for recurrent or metastatic breast cancer; OR
  - **84. ii.** Approve for 1 year (total) if Kadcyla will be used as adjuvant therapy; AND
- **K)** The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

69. Non-Small Cell Lung Cancer Approve for 1 year if the patient meets the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has metastatic disease; AND
- **C)** The disease has activating human epidermal growth factor receptor 2 (HER2)-mutations; AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

85.

70. Salivary Gland Tumor. Approve for 1 year if the patient meets the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has recurrent, unresectable, or metastatic disease; AND
- **C)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kadcyla is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

274. Kadcyla® intravenous infusion [prescribing information]. South San Francisco, CA: Genentech; February 2022.
275. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – March 23, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed August 22, 2023.
276. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on August 22, 2023. Search term: ado-trastuzumab emtansine.
277. The NCCN Head and Neck Cancers Clinical Practice Guidelines in Oncology (version 2.2023– May 15, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on August 22, 2023.
278. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – April 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on August 22, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Kimmtrak Prior Authorization Policy
- Kimmtrak® (tebentafusp-tebn intravenous infusion – Immunocore)

REVIEW DATE: 02/08/2023

OVERVIEW
Kimmtrak, a bispecific gp100 peptide-human leukocyte antigen (HLA)-directed CD3 T cell engager, is indicated for the treatment of adults with HLA-A*02:01-positive, unresectable or metastatic uveal melanoma.[1]

Guidelines
The National Comprehensive Cancer Network melanoma: uveal (version 2.2022 – April 5, 2022) clinical practice guidelines recommend Kimmtrak as a preferred regimen for patients with distant metastatic disease who are HLA-A*02:01 positive (category 1).[2,3]

Safety
Kimmtrak has a Boxed Warning for cytokine release syndrome which may be serious or life-threatening.[1]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Kimmtrak. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kimmtrak as well as the monitoring required for adverse events and long-term efficacy, approval requires Kimmtrak to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Kimmtrak is recommended in those who meet the following criteria:

FDA-Approved Indication

30. Uveal Melanoma. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has unresectable or metastatic disease; AND
- **C)** The tumor is HLA-A*02:01 positive; AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kimmtrak is not recommended in the following situations:

307. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

968. Kimmtrak intravenous infusion [prescribing information]. Conshohocken, PA: Immunocore; November 2022.
969. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 3 2023. Search term: tebentafusp.
970. The NCCN Melanoma: Uveal Clinical Practice Guidelines in Oncology (version 2.2022 – April 5, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 3, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Kyprolis Prior Authorization Policy
- Kyprolis (carfilzomib intravenous infusion – Amgen/Onyx)

REVIEW DATE: 04/12/2023

OVERVIEW

Kyprolis, a proteasome inhibitor, is approved for **multiple myeloma** in the following situations:[1]

- for relapsed or refractory disease, in combination with dexamethasone ± lenalidomide or Darzalex (daratumumab intravenous infusion)/dexamethasone, Darzalex Faspro (daratumumab and hyaluronidase-fihj subcutaneous injection)/dexamethasone, or with Sarclisa (isatuximab-irfc intravenous infusion)/dexamethasone in patients who have received one to three lines of previous therapy.
- for relapsed or refractory disease, as a single agent in those who have received one or more lines of therapy.

Guidelines

Kyprolis is discussed in guidelines from the National Comprehensive Cancer Network (NCCN).[2]

- **Multiple Myeloma:** The NCCN guidelines (version 3.2023 – December 8, 2022) recommend multiple therapeutic regimens that may be used for primary therapy and previously treated multiple myeloma.[3] For transplant and non-transplant candidates, Kyprolis/lenalidomide/dexamethasone is recommended as preferred regimen for primary treatment, and Kyprolis/cyclophosphamide/dexamethasone is among the regimens that are useful in certain circumstances. Additionally, Kyprolis/Darzalex/dexamethasone is listed as useful in certain circumstances as primary therapy for transplant candidates. For previously treated multiple myeloma, multiple preferred regimens are listed, including Kyprolis/lenalidomide/dexamethasone, Kyprolis/Sarclisa/dexamethasone, and Kyprolis/Darzalex/dexamethasone. Additionally, there are multiple Kyprolis-containing regimens recommended as other or useful in certain circumstances.
- **Systemic Light Chain Amyloidosis:** The NCCN guidelines (version 2.2023 – November 28, 2022) list Kyprolis ± dexamethasone as a therapy for previously treated disease, for patients with non-cardiac amyloidosis.[6] Of note, cardiac toxicity and hypertension are among the Warnings listed for Kyprolis.[1]
- **Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma:** In NCCN guidelines (version 1.2023 – July 6, 2022), Kyprolis/rituximab/dexamethasone is listed among other recommended regimens for primary treatment of Waldenstrom's Macroglobulinemia/lymphoplasmacytic lymphoma.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Kyprolis. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kyprolis as well as the monitoring required for adverse events and long-term efficacy, approval requires Kyprolis to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kyprolis is recommended in those who meet one of the following criteria:

FDA-Approved Indication

33. Multiple Myeloma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **43.** Patient is ≥ 18 years of age; AND
- **44.** Patient meets ONE of the following (i or ii):
  - **A)** Kyprolis will be used in combination with lenalidomide or cyclophosphamide and dexamethasone; OR
  - **B)** Patient has tried at least ONE prior regimen for multiple myeloma; AND
    Note: Examples include bortezomib, lenalidomide, cyclophosphamide, Darzalex (daratumumab intravenous infusion), Ninlaro (ixazomib capsules).
- **45.** The medication is prescribed by or in consultation with an oncologist or a hematologist.

Other Uses with Supportive Evidence

34. Light Chain Amyloidosis. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
- **D)** Patient is ≥ 18 years of age; AND
- **E)** Patient has non-cardiac amyloidosis; AND
- **F)** Patient has received at least one other regimen for this condition; AND
  Note: Examples of agents used in other regimens include bortezomib, lenalidomide, cyclophosphamide, and melphalan.
- **G)** The medication is prescribed by or in consultation with an oncologist or a hematologist.

35. Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The medication will be used in combination with a rituximab product and dexamethasone; AND
- **C)** The medication is prescribed by or in consultation with an oncologist or a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kyprolis is not recommended in the following situations:

308. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

47. Kyprolis® intravenous infusion [prescribing information]. Onyx/Amgen: Thousand Oaks, CA; June 2022.
48. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 9, 2023. Search term: carfilzomib.
49. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 3.2023 – December 8, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 9, 2023.
50. The NCCN Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma Clinical Practice Guidelines in Oncology (version 1.2023 – July 6, 2022). © 2022

National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 9, 2023.
51. Treon SP, Tripsas CK, Meid K, et al. Carfilzomib, rituximab, and dexamethasone (CaRD) treatment offers a neuropathy-sparing approach for treating Waldenström's macroglobulinemia. *Blood*. 2014;124(4):503-510.
52. The NCCN Systemic Light Chain Amyloidosis Clinical Practice Guidelines in Oncology (version 2.2023 – November 28, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 9, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Levoleucovorin Products Prior Authorization Policy
- Fusilev® (levoleucovorin intravenous infusion – Spectrum)
- Khapzory™ (levoleucovorin intravenous infusion – Spectrum)
- Levoleucovorin intravenous infusion – various manufacturers

REVIEW DATE: 06/28/2023

OVERVIEW

Levoleucovorin (Fusilev, Khapzory, generic) is indicated for the following uses:[1,2]
- **Colorectal cancer**, in advanced metastatic disease for use in combination chemotherapy with 5-fluorouracil.
- **Impaired methotrexate elimination** or overdosage of folic acid antagonists.
- **Osteosarcoma**, for rescue after high-dose methotrexate therapy.

Levoleucovorin is the pharmacologically active, levo-isomer of racemic *d,l*-leucovorin.[1,2] Levoleucovorin is a chemically reduced derivative of folic acid, which can counteract the toxic and therapeutic effects of folic acid antagonists, such as methotrexate. In addition, levoleucovorin can enhance the therapeutic and toxic effects of fluoropyrimidines used in oncology.

Guidelines

The National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium recommends levoleucovorin use in combination with methotrexate for the treatment of gestational trophoblastic neoplasia, T-cell lymphomas, central nervous system cancers, B-cell lymphomas, chronic lymphocytic leukemia/small lymphocytic lymphoma, acute lymphoblastic leukemia, pediatric aggressive mature B-cell lymphomas, blastic plasmacytoid dendritic cell neoplasm, osteosarcoma, and Waldenstrom macroglobulinemia.[3] The NCCN Compendium recommends levoleucovorin use in combination with fluorouracil-based chemotherapy for the treatment of occult primary cancer, neuroendocrine and adrenal tumors, biliary tract cancers, ovarian/fallopian tube/primary peritoneal cancer, thymomas and thymic carcinomas, esophageal and esophagogastric junction cancer, anal cancer, colon cancer, gastric cancer, small bowel adenocarcinoma, ampullary cancer, cervical cancer, rectal cancer, pancreatic adenocarcinoma, and bladder cancer.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of levoleucovorin. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with levoleucovorin as well as the monitoring required for adverse events and long-term efficacy, approval requires levoleucovorin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of levoleucovorin is recommended in those who meet one of the following:

FDA-Approved Indications

31. Colon or Rectal Carcinoma. Approve for 1 year if the patient meets the following (A and B):
- **A)** Levoleucovorin is used in combination with fluorouracil-based chemotherapy; AND
- **B)** Levoleucovorin is prescribed by or in consultation with an oncologist.

32. Methotrexate Overdosage, or Impaired Methotrexate Elimination. Approve for 1 month.

33. Osteosarcoma. Approve for 1 year if the patient meets the following (A and B):
- **A)** Levoleucovorin is used in combination with high-dose methotrexate; AND
- **B)** Levoleucovorin is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

34. Cancer Diagnosis Currently Being Treated With Methotrexate. Approve for 1 year if levoleucovorin is prescribed by or in consultation with an oncologist.
Note: Examples include T-cell lymphoma, B-cell lymphoma, gestational trophoblastic neoplasm, central nervous system cancer.

35. Cancer Diagnosis Currently Being Treated With 5-Fluorouracil. Approve for 1 year if levoleucovorin is prescribed by or in consultation with an oncologist.
Note: Examples include ovarian cancer, gastric cancer, cervical cancer.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of levoleucovorin is not recommended in the following situations:

309. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

971. Fusilev® intravenous infusion [prescribing information]. Irvine, CA: Spectrum Pharmaceuticals; November 2020.
972. Khapzory™ intravenous infusion [prescribing information]. Irvine, CA: Spectrum Pharmaceuticals; March 2020.
973. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 22, 2023. Search term: levoleucovorin.
974. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 22, 2023.
975. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – May 26, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 22, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Lumoxiti Prior Authorization Policy
- Lumoxiti® (moxetumomab pasudotox-tdfk intravenous infusion – AstraZeneca)

REVIEW DATE: 10/11/2023

OVERVIEW

Lumoxiti, a CD22-directed cytotoxin, is indicated for the treatment of adults with relapsed or refractory **hairy cell leukemia** who received at least two prior systemic therapies, including treatment with a purine nucleoside analog.[1] AstraZeneca will permanently withdraw Lumoxiti from the market in July 2023. This is due to very low uptake of Lumoxiti and the availability of other treatment options. As such, physicians should not start new patients on Lumoxiti.

Limitations of Use: Lumoxiti is not recommended for use in patients with a creatinine clearance ≤ 29 mL/min.

Guidelines

The National Comprehensive Cancer Network guidelines for Hairy Cell Leukemia (version 1.2023 – August 30, 2022) recommend purine nucleoside analogs (cladribine or pentostatin) as first-line agents for hairy cell leukemia.[2,3] Lumoxiti is recommended as a single agent for the treatment of progression of hairy cell leukemia after therapy for relapsed/refractory disease.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lumoxiti. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lumoxiti as well as the monitoring required for adverse events and long-term efficacy, approval requires Lumoxiti to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lumoxiti is recommended in those who meet the following criteria:

FDA-Approved Indication

36. Hairy Cell Leukemia. Approve for 6 months if the patient meets the following (A, B, C, D, and E):
- **M)** Patient is currently receiving Lumoxiti; AND
- **N)** Patient is ≥ 18 years of age; AND
- **O)** Patient has received ≥ 2 prior systemic therapies, including therapy with a purine analog; AND
  Note: Purine analogs include cladribine and pentostatin.
- **P)** Patient has an estimated creatinine clearance ≥ 30 mL/min; AND
- **Q)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lumoxiti is not recommended in the following situations:

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

976. Lumoxiti® intravenous infusion [prescribing information]. Wilmington, DE: AstraZeneca; August 2020.
977. The NCCN Hairy Cell Leukemia Clinical Practice Guidelines in Oncology (version 1.2023 – August 30, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed October 5, 2023.
978. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 5, 2023. Search term: moxetumomab.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Lunsumio Prior Authorization Policy
- Lunsumio™ (mosunetuzumab-axgb intravenous infusion – Genentech)

REVIEW DATE: 01/11/2023

OVERVIEW
Lunsumio, a bispecific CD20-directed CD3 T-cell engager, is indicated for the treatment of adults with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy.[1]

Guidelines
The National Comprehensive Cancer Network has not addressed Lunsumio.

Safety
Lunsumio has a Boxed Warning for cytokine release syndrome.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Lunsumio. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lunsumio as well as the monitoring required for adverse events and long-term efficacy, approval requires Lunsumio to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Lunsumio is recommended in those who meet the following criteria:

FDA-Approved Indication

36. Follicular Lymphoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has received ≥ two lines of systemic therapy; AND
  Note: Examples of systemic therapy include CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) plus rituximab or Gazyva (obinutuzumab intravenous infusion) and CVP (cyclophosphamide, vincristine, prednisone) plus rituximab or Gazyva.
- **C)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Lunsumio is not recommended in the following situations:

310. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

979. Lunsumio intravenous infusion [prescribing information]. South San Francisco, CA: Genentech; December 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Margenza Prior Authorization Policy
- Margenza® (margetuximab-cmbk intravenous infusion – MacroGenics)

REVIEW DATE: 02/22/2023

OVERVIEW

Margenza, a human epidermal growth factor receptor 2 (HER2)/neu receptor antagonist, in combination with chemotherapy, is indicated for the treatment of metastatic human epidermal growth factor receptor 2 (**HER2**)**-positive breast cancer** in adults who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) breast cancer guidelines (version 2.2023 – February 7, 2023) recommend Margenza as a fourth-line and beyond treatment for recurrent unresectable (local or regional) or stage IV disease. Margenza should be used in combination with chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine). Other fourth-line and beyond therapies include trastuzumab + docetaxel or vinorelbine; trastuzumab + paclitaxel ± carboplatin; capecitabine + trastuzumab or lapatinib; trastuzumab + lapatinib (without cytotoxic therapy); trastuzumab + other chemotherapy agents; and Nerlynx® (neratinib tablets) + capecitabine. NCCN recommends the following therapies as first-line: Perjeta® (pertuzumab intravenous infusion) + trastuzumab + docetaxel; and Perjeta + trastuzumab + paclitaxel. Enhertu® (fam-trastuzumab deruxtecan-nxki intravenous infusion) is the recommended therapy for second-line use. Recommended third-line therapies are Tukysa® (tucatinib tablets) + trastuzumab + capecitabine or Kadcyla® (ado-trastuzumab emtansine intravenous infusion).

Safety

Margenza has a Boxed Warning regarding left ventricular dysfunction and embryo-fetal toxicity.[1] Margenza may lead to reductions in left ventricular ejection fraction; treatment should be discontinued for a confirmed clinically significant decrease in left ventricular function. Exposure to Margenza during pregnancy can cause embryo-fetal harm; patients should be advised of the risk and need for effective contraception.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Margenza. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Margenza as well as the monitoring required for adverse events and long-term efficacy, approval requires Margenza to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Margenza is recommended in those who meet the following criteria:

FDA-Approved Indication

71. Breast Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, D, E, F, and G):

A) Patient is ≥ 18 years of age; AND

B) Patient has recurrent or metastatic disease; AND

C) Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND

D) Patient has tried at least three prior anti-HER2 regimens; AND

- Note: Some examples of anti-HER2 regimens are Perjeta (pertuzumab intravenous infusion) + trastuzumab + docetaxel, Perjeta + trastuzumab + paclitaxel; Kadcyla (ado-trastuzumab emtansine intravenous infusion), Enhertu (fam-trastuzumab deruxtecan-nxki intravenous infusion), Tukysa (tucatinib tablets) + trastuzumab + capecitabine, trastuzumab + lapatinib, trastuzumab + docetaxel, trastuzumab + vinorelbine, Nerlynx (neratinib tablets) + capecitabine.

E) At least one of the prior anti-HER2 regimens was used for metastatic disease; AND

F) The medication is used in combination with chemotherapy; AND

- Note: Examples of chemotherapy are capecitabine, eribulin, gemcitabine, vinorelbine.

G) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Margenza is not recommended in the following situations:

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

32. Margenza® intravenous infusion [prescribing information]. Rockville, MD: MacroGenics; December 2020.
33. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – February 7, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 15, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Monjuvi Prior Authorization Policy
- Monjuvi® (tafasitamab-cxix intravenous infusion – MorphoSys/Incyte)

REVIEW DATE: 09/06/2023

OVERVIEW

Monjuvi, a CD19-directed antibody-drug conjugate, is indicated in combination with lenalidomide for adults with relapsed or refractory **diffuse large B-cell lymphoma** (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant.[1] Monjuvi is administered as a weight-based intravenous infusion. It should be given in combination with lenalidomide for a maximum of 12 cycles, then as monotherapy until disease progression or unacceptable toxicity.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for B-cell lymphomas (version 5.2023 – July 7, 2023) include Monjuvi + lenalidomide among the alternatives for second-line and subsequent therapy of DLBCL, follicular lymphoma, histologic transformation of indolent lymphomas to DLBCL, human immunodeficiency virus (HIV)-related B-cell lymphoma, post-transplant lymphoproliferative disorders, and high-grade B-cell lymphoma.[2,3] NCCN also notes that it is unclear if Monjuvi would have a negative impact on the efficacy of subsequent anti-CD19 CAR T-cell therapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Monjuvi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Monjuvi as well as the monitoring required for adverse events and long-term efficacy, approval requires Monjuvi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Monjuvi is recommended in those who meet one of the following criteria:

FDA-Approved Indication

37. Diffuse Large B-Cell Lymphoma. Approve for 1 year if the patient meets the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has been treated with at least one prior chemotherapy regimen; AND
- **C)** According to the prescriber, the patient is not eligible for autologous stem cell transplant; AND
- **D)** Patient meets one of the following (i or ii):
  - **i.** Monjuvi will be used in combination with Revlimid (lenalidomide capsules); OR
  - **ii.** Patient has already received 12 cycles of Monjuvi; AND
- **E)** The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

38. B-Cell Lymphoma. Approve for 1 year if the patient meets the following (A, B, C, D, and E):
Note: Examples include follicular lymphoma, high-grade B-cell lymphoma, HIV-related B-cell lymphoma, post-transplant lymphoproliferative disorders, histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma.

G) Patient is ≥ 18 years of age; AND

H) Patient has been treated with at least one prior chemotherapy regimen; AND

Note: Examples of chemotherapy regimens include CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) plus rituximab or Gazyva (obinutuzumab intravenous infusion), CVP (cyclophosphamide, vincristine, prednisone) plus rituximab or Gazyva, or lenalidomide plus rituximab.

I) According to the prescriber, the patient is not eligible for autologous stem cell transplant; AND

J) Patient meets one of the following (i or ii):

i. Monjuvi will be used in combination with Revlimid (lenalidomide capsules); OR

ii. Patient has already received 12 cycles of Monjuvi; AND

K) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Monjuvi is not recommended in the following situations:

311. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

980. Monjuvi® intravenous infusion [prescribing information]. Boston, MA: MorphoSys/Incyte; June 2021.
981. The NCCN B-Cell Lymphoma Clinical Practice Guidelines in Oncology (version 5.2023 – July 7, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 1, 2023.
982. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 1, 2023. Search term: tafasitamab.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Mylotarg Prior Authorization Policy
- Mylotarg™ (gemtuzumab ozogamicin intravenous infusion – Pfizer)

REVIEW DATE: 07/12/2023

OVERVIEW

Mylotarg, an antibody-drug conjugate directed towards the CD33 antigen, is indicated for the following:[1]

- **CD33-positive acute myeloid leukemia (AML)**, newly diagnosed, in adults and pediatric patients ≥ 1 month of age; AND
- **CD33-positive AML**, relapsed or refractory, in adults and in pediatric patients ≥ 2 years of age.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for **AML** (version 3.2023 – April 5, 2023) recommend Mylotarg for induction therapy, post-remission therapy, and for relapsed/refractory CD33-positive AML.[2,3] Mylotarg can be used as a single agent or in combination with cytarabine and daunorubicin. The NCCN guidelines for AML also recommend Mylotarg in patients ≥ 18 years of age for induction and consolidation therapy for acute promyelocytic leukemia, and for relapsed disease. Mylotarg can be used in combination with tretinoin and/or arsenic trioxide.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Mylotarg. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Mylotarg as well as the monitoring required for adverse events and long-term efficacy, approval requires Mylotarg to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mylotarg is recommended in those who meet one of the following criteria:

FDA-Approved Indication

37. Acute Myeloid Leukemia. Approve for the duration noted if the patient meets ONE of the following (A or B):

L) Newly diagnosed CD33-positive disease: Approve for 1 year if the patient meets the following (i and ii):
- **i.** Patient is ≥ 1 month of age; AND
- **ii.** Mylotarg is prescribed by or in consultation with an oncologist; OR

M) Relapsed or refractory CD33-positive disease: Approve for 1 month if the patient meets the following (i and ii):
- **i.** Patient is ≥ 2 years of age; AND
- **ii.** Mylotarg is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

38. Acute Promyelocytic Leukemia. Approve for 6 months if the patient meets the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Mylotarg is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mylotarg is not recommended in the following situations:

312. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

983. Mylotarg™ intravenous infusion [prescribing information]. Philadelphia, PA: Pfizer; August 2021.
984. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 3.2023 – April 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 7, 2023.
985. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 7, 2023. Search term: gemtuzumab.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Oncaspar Prior Authorization Policy
- Oncaspar® (pegaspargase intramuscular or intravenous injection – Servier)

REVIEW DATE: 05/31/2023

OVERVIEW

Oncaspar a conjugate of *Escherichia coli*-derived L-asparaginase and monomethoxypolyethylene glycol (mPEG), is indicated as a component of a multi-agent chemotherapy regimen for first-line treatment of **acute lymphoblastic leukemia** (ALL) in pediatric and adult patients and patients with ALL with hypersensitivity to asparaginase.[1]

Guidelines

Oncaspar is addressed in National Comprehensive Cancer Network (NCCN) guidelines:

- **ALL:** The NCCN guidelines for **ALL** (version 1.2022 – April 4, 2022) and for **Pediatric ALL** (version 2.2023 – March 10, 2023) recommend pegaspargase as a component of a multi-agent chemotherapeutic regimen for induction/consolidation therapy for ALL, for induction therapy in Philadelphia chromosome-negative ALL in patients ≥ 65 years of age, for relapsed/refractory Philadelphia chromosome-negative ALL, and relapsed/refractory Philadelphia chromosome-positive ALL.[2,3,5]
- **T-Cell Lymphomas:** The NCCN guidelines (version 1.2023 – January 5, 2023) recommend pegaspargase as a component of therapy for extranodal NK/T-cell lymphoma and as an alternative induction regimen if no response or progressive disease after primary treatment for hepatosplenic T-cell lymphoma.[3,4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Oncaspar. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Oncaspar as well as the monitoring required for adverse events and long-term efficacy, approval requires Oncaspar to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Oncaspar is recommended in those who meet one of the following criteria:

FDA-Approved Indication

39. Acute Lymphoblastic Leukemia. Approve for 1 year if the patient meets BOTH of the following criteria (A and B):
- **A)** Patient is ≥ 1 month of age; AND
- **B)** Oncaspar is prescribed by or consultation with an oncologist.

Other Uses with Supportive Evidence

40. Extranodal NK/T-cell Lymphoma. Approve for 1 year if the patient meets BOTH of the following criteria (A and B):
- **A)** Patient is ≥ 8 years of age; AND
- **B)** Oncaspar is prescribed by or in consultation with an oncologist.

41. Hepatosplenic T-cell Lymphoma. Approve for 1 year if the patient meets ALL of the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient had no response or progressive disease after primary treatment; AND
- **C)** Oncaspar is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Oncaspar is not recommended in the following situations:

313. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

986. Oncaspar® intramuscular and intravenous injection [prescribing information]. Boston, MA: Servier; December 2022.
987. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 1.2022 – April 4, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 16, 2022.
988. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 9, 2023. Search term: pegaspargase.
989. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 9, 2023.
990. The NCCN Pediatric Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 2.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 9, 2023.
991. Zhao Q, Fan S, Chang Y, et al. Clinical efficacy of cisplatin, dexamethasone, gemcitabine and pegaspargase (DDGP) in the initial treatment of advanced stage (stage III-IV) extranodal NK/T-cell lymphoma, and its correlation with Epstein-Barr virus. *Cancer Manag Res*. 2019;11:3555-3564.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Onivyde Prior Authorization Policy
- Onivyde® (irinotecan liposome intravenous infusion – Ipsen)

REVIEW DATE: 04/19/2023

OVERVIEW

Onivyde, a topoisomerase inhibitor, is indicated, in combination with fluorouracil and leucovorin, for the treatment of **metastatic adenocarcinoma of the pancreas** after disease progression in patients following gemcitabine-based therapy.[1] Limitation of use: Onivyde is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

Guidelines

The National Comprehensive Cancer Network has addressed Onivyde for the following indications:

- **Ampullary adenocarcinoma:** Clinical practice guidelines (version 2.2022 – December 6, 2022) recommend Onivyde, in combination with fluorouracil and leucovorin, for the subsequent treatment of disease progression in patients with pancreatobiliary and mixed type disease with good performance status (defined as Eastern Cooperative Oncology Group [ECOG] performance status of 0 or 1, good biliary drainage, and adequate nutritional intake) [category 2A].[3,4]
- **Biliary tract cancers:** Clinical practice guidelines (version 1.2023 – March 10, 2023) recommend Onivyde in combination with fluorouracil and leucovorin for the subsequent treatment of unresectable, resected gross residual, or metastatic biliary tract cancers (category 2B).[3,5]
- **Pancreatic adenocarcinoma:** Clinical practice guidelines (version 2.2022 – December 6, 2022) recommend Onivyde, in combination with fluorouracil and leucovorin, for the subsequent treatment of locally advanced (category 2A), or metastatic (category 1) pancreatic adenocarcinoma in patients with ECOG performance status of 0 to 2.[2,3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Onivyde. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Onivyde as well as the monitoring required for adverse events and long-term efficacy, approval requires Onivyde to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Onivyde is recommended in those who meet one of the following criteria:

FDA-Approved Indication

42. Pancreatic Adenocarcinoma. Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has locally advanced or metastatic disease; AND

C) Patient has tried at least one of the following chemotherapy regimens for pancreatic adenocarcinoma (i or ii):
  i. Gemcitabine-based chemotherapy; OR
  ii. Fluoropyrimidine-based chemotherapy without irinotecan; AND
D) Onivyde will be used in combination with fluorouracil and leucovorin; AND
E) Onivyde is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

43. Ampullary Adenocarcinoma. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has tried at least ONE of the following chemotherapy regimens (i, ii, or iii):
  i. Gemcitabine-based therapy; OR
  ii. Fluoropyrimidine-based therapy, if no prior irinotecan; OR
  iii. Oxaliplatin-based therapy, if no prior irinotecan; AND
C) Onivyde will be used in combination with fluorouracil and leucovorin; AND
D) Onivyde is prescribed by or in consultation with an oncologist.

44. Biliary Tract Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has one of the following (i, ii, or iii):
  i. Gallbladder cancer; OR
  ii. Extrahepatic cholangiocarcinoma; OR
  iii. Intrahepatic cholangiocarcinoma; AND
C) Patient has disease progression on or after systemic therapy; AND
  Note: Examples of systemic therapy include gemcitabine, cisplatin, fluorouracil, and capecitabine.
D) Onivyde is used in combination with fluorouracil and leucovorin; AND
E) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage for Onivyde is not recommended in the following situations:

314. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

992. Onivyde® liposome intravenous infusion [prescribing information]. Basking Ridge, NJ: Ipsen; February 2023.
993. The NCCN Pancreatic Adenocarcinoma Clinical Practice Guidelines in Oncology (version 2.2022 – December 6, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed April 11, 2023.
994. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 11, 2023. Search term: irinotecan liposome.
995. The NCCN Ampullary Adenocarcinoma Clinical Practice Guidelines in Oncology (version 2.2022 – December 6, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed April 11, 2023.
996. The NCCN Biliary Tract Cancers Clinical Practice Guidelines in Oncology (version 1.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 11, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Padcev Prior Authorization Policy
- Padcev™ (enfortumab vedotin-ejfv intravenous infusion – Astellas and Seagen)

REVIEW DATE: 12/21/2022

OVERVIEW

Padcev, an antibody-drug conjugate, is indicated for the treatment of adult patients with locally advanced or metastatic **urothelial cancer** who:[1]

- Have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor, and platinum-containing chemotherapy.
- Are ineligible for cisplatin-containing chemotherapy and have previously received ≥ one prior line of therapy.

Guidelines

The National Comprehensive Cancer Network (NCCN) **bladder cancer** clinical practice guidelines (version 2.2022 – May 20, 2022) recommend Padcev for the subsequent treatment of locally advanced or metastatic urothelial carcinoma of the bladder, upper genitourinary tract, prostate, and urethra.[2,3] Patients should have previously received platinum-containing chemotherapy, a checkpoint inhibitor, platinum-containing chemotherapy plus a checkpoint inhibitor, or first-line therapy with agents other than platinum or a checkpoint inhibitor.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Padcev. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Padcev as well as the monitoring required for adverse events and long-term efficacy, approval requires Padcev to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Padcev is recommended in those who meet the following criteria:

FDA-Approved Indication

45. Urothelial Carcinoma. Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has locally advanced or metastatic disease; AND
- **C)** Patient has tried at least one other systemic therapy; AND
- **D)** Padcev is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Padcev is not recommended in the following situations:

315. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

997. Padcev™ intravenous infusion [prescribing information]. Northbrook, IL: Astellas Pharma; October 2022.
998. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (version 2.2022 – May 20, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 19, 2022.
999. The NCCN Drugs and Biologics Compendium. © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 19, 2022. Search term: enfortumab.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Perjeta Prior Authorization Policy
- Perjeta® (pertuzumab intravenous infusion –Genentech)

REVIEW DATE: 07/19/2023

OVERVIEW

Perjeta, a human epidermal growth factor receptor 2 (HER2) antagonist, is indicated for the treatment of **HER2-positive breast cancer** for the following uses:[1]

- **Adjuvant treatment,** of patients with early disease at high risk of recurrence, in combination with trastuzumab and chemotherapy.
- **Metastatic disease,** in combination with trastuzumab and docetaxel in patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.
- **Neoadjuvant treatment,** of patients with locally advanced, inflammatory, or early stage disease (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer, in combination with trastuzumab and chemotherapy.

Guidelines

Perjeta is discussed in the guidelines from the National Comprehensive Cancer Network (NCCN):

- **Breast Cancer**: NCCN guidelines (version 4.2023 – March 23, 2023) recommend Perjeta in the preoperative/adjuvant and metastatic setting.[2,3] For preoperative (neoadjuvant)/adjuvant therapy in HER2-positive disease, docetaxel + carboplatin + trastuzumab + Perjeta is a "Preferred Regimen" (category 1); doxorubicin + cyclophosphamide followed by paclitaxel + trastuzumab and Perjeta is recommended as "Useful in Certain Circumstances" (category 2A). Under "Other Recommended Regimens", doxorubicin + cyclophosphamide followed by docetaxel + trastuzumab + Perjeta is also listed (category 2A). In the neoadjuvant/adjuvant setting, the chemotherapy agents in combination with trastuzumab + Perjeta are administered for usually four cycles, followed by trastuzumab ± Perjeta to complete 1 year of therapy. If no residual disease after preoperative therapy or no preoperative therapy, the guidelines recommends to complete up to one year of HER2 targeted therapy with trastuzumab ± Perjeta after completing planned chemotherapy regimen course. In the metastatic setting, the "Preferred Regimens" are Perjeta + trastuzumab + docetaxel (category 1) or Perjeta + trastuzumab + paclitaxel (category 2A). In this setting, chemotherapy + trastuzumab + Perjeta is continued until disease progression or unmanageable toxicity.
- **Colon Cancer/Rectal Cancer**: NCCN guidelines (version 2.2023 – April 25, 2023) for colon cancer and rectal cancer (version 3.2023 – May 26, 2023) recommend use of Perjeta + trastuzumab in patients with HER2-amplified, *RAS* and *BRAF* wild-type, colon and rectal cancer.[3-5] Perjeta is recommended for use in a variety of therapy settings (e.g., adjuvant therapy, primary treatment, subsequent therapy) + trastuzumab, in patients who are not appropriate for intensive therapy and with no previous treatment with a HER2 inhibitor. It is a category 2A recommendation for primary and subsequent therapy settings; category 2B recommendation for adjuvant therapy.
- **Head and Neck Cancers:** NCCN guidelines (version 2.2023 – May 15, 2023) recommend Perjeta + trastuzumab as a systemic therapy option for recurrent, unresectable, or metastatic salivary gland tumors, (Useful in Certain Circumstances), for HER2 positive tumors (category 2A).[3,6]
- **Biliary Tract Cancers:** NCCN guidelines (version 2.2023 – May 10, 2023) recommend Perjeta + trastuzumab as subsequent treatment for biliary tract cancers for progression on or after systemic

treatment for unresectable or metastatic disease that is HER2-positive as "Useful in Certain Circumstances" (category 2A).[7]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Perjeta. All approvals are provided for the duration noted below. Because of the specialized skills required for the evaluation and diagnosis of patients treated with Perjeta, as well as the monitoring required for the adverse events and long-term efficacy, approval requires Perjeta to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Perjeta is recommended in those who meet one of the following criteria:

FDA-Approved Indications

72. Breast Cancer – Neoadjuvant or Adjuvant Therapy. Approve for 1 year (total) if the patient meets the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **C)** Patient meets ONE of the following (i or ii):
  - **i.** The medication will be used in combination with chemotherapy; OR
    RRRR) Note: Examples of chemotherapy include doxorubicin, cyclophosphamide, docetaxel, paclitaxel, carboplatin.
  - **ii.** The medication is continued after chemotherapy to complete 1 year of neoadjuvant or adjuvant therapy; AND
- **D)** Perjeta will be used in combination with a trastuzumab product; AND
- **E)** The medication is prescribed by or in consultation with an oncologist.

2. Breast Cancer – Metastatic Disease. Approve for 1 year if the patient meets all of the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **C)** Patient has not been previously treated with anti-HER2 therapy or chemotherapy for metastatic disease; AND
- **D)** The medication will be used in combination with trastuzumab and chemotherapy; AND
  SSSS) Note: Examples of chemotherapy are docetaxel, paclitaxel.
- **E)** The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

3. Biliary Tract Cancer. Approve for 1 year if the patient meets the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **C)** Patient has tried at least one systemic chemotherapy regimen; AND

Note: Examples of a systemic chemotherapy regimen include: gemcitabine and cisplatin; Imfinzi (durvalumab intravenous infusion) and gemcitabine, 5-flourouracil and oxaliplatin, capecitabine and oxaliplatin, gemcitabine and cisplatin.

D) Perjeta will be used in combination with a trastuzumab product; AND
E) The medication is prescribed by or in consultation with an oncologist.

4. **Colon or Rectal Cancer.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
   C) The medication is used in combination with trastuzumab; AND
   D) The medication is prescribed by or in consultation with an oncologist.

5. **Salivary Gland Tumor**. Approve for 1 year if the patient meets the following (A, B, C, D, and E):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has recurrent, unresectable, or metastatic disease; AND
   C) Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
   D) The medication is used in combination with trastuzumab; AND
   E) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Perjeta is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

279. Perjeta® intravenous infusion [prescribing information]. South San Francisco, CA: Genentech; February 2021.
280. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – March 23, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 17, 2023
281. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 17, 2023. Search term: pertuzumab.
282. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 17, 2023.
283. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – May 26, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 17, 2023.
284. The NCCN Head and Neck Cancers Clinical Practice Guidelines in Oncology (version 2.2023 – May 15, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 17, 2023.
285. The NCCN Biliary Tract Cancers Clinical Practice Guidelines in Oncology (version 2.2023 – May 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 17, 2023.

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PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Phesgo Prior Authorization Policy
- Phesgo® (pertuzumab, trastuzumab, and hyaluronidase-zzxf subcutaneous injection – Genentech)

REVIEW DATE: 07/12/2023

OVERVIEW

Phesgo, a combination of pertuzumab, trastuzumab, and hyaluronidase-zzxf, is indicated for the following uses:[1]

- **Early breast cancer**, for use in combination with chemotherapy for the neoadjuvant treatment of adults with human epidermal growth factor receptor 2 (HER2)-positive, locally advanced, inflammatory, or early stage breast cancer (either > 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. It is also indicated for the adjuvant treatment of adults with HER2-positive early breast cancer at high risk of recurrence.
- **Metastatic breast cancer**, for use in combination with docetaxel for the treatment of adults with HER2-positive disease who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

7. Patients should be selected for therapy based on an FDA-approved companion diagnostic test.

Guidelines

- National Comprehensive Cancer Network (NCCN) guidelines for **breast cancer** (version 4.2023 – March 23, 2023) note that Phesgo may be substituted anywhere that the combination of Perjeta® (pertuzumab intravenous [IV] infusion) and trastuzumab IV are given as part of systemic therapy.[2] The guidelines note that Phesgo has different dosing and administration instructions compared with the IV products. For preoperative (neoadjuvant)/adjuvant therapy in HER2-positive disease, docetaxel + carboplatin + trastuzumab + Perjeta is a preferred regimen (category 2A). There are also other chemotherapy regimens listed that are used with trastuzumab + Perjeta. In the neoadjuvant/adjuvant setting, HER-2 targeted therapy is given for up to 1 year. In the recurrent unresectable (local or regional) or metastatic setting, the preferred regimens are Perjeta + trastuzumab + docetaxel (category 1) or Perjeta + trastuzumab + paclitaxel (category 2A). In this setting, chemotherapy + trastuzumab + Perjeta is continued until disease progression or unmanageable toxicity.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Phesgo. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Phesgo, as well as the monitoring required for adverse events and long-term efficacy, approval requires Phesgo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Phesgo is recommended in those who meet one of the following criteria:

FDA-Approved Indications

73. Breast Cancer – Neoadjuvant or Adjuvant Therapy. Approve for 1 year (total) if the patient meets all of the following (A, B, C, and D):

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **C)** Patient meets one of the following (i or ii):
  - **i.** The medication will be used in combination with chemotherapy; OR
    Note: Examples of chemotherapy are doxorubicin, cyclophosphamide, docetaxel, paclitaxel, carboplatin.
  - **ii.** Phesgo is continued after chemotherapy to complete 1 year of neoadjuvant or adjuvant therapy; AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

2. Breast Cancer – Metastatic Disease. Approve for 1 year if the patient meets all of the following (A, B, C, D, and E):

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **C)** Patient has not been previously treated with anti-HER2 therapy or chemotherapy for metastatic disease; AND
- **D)** The medication will be used in combination with chemotherapy; AND
  Note: Examples of chemotherapy are docetaxel, paclitaxel.
- **E)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Phesgo is not recommended in the following situations:

8. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

34. Phesgo® subcutaneous injection [prescribing information]. South San Francisco, CA: Genentech; June 2020.
35. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – March 23, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 10, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Polivy Prior Authorization Policy
- Polivy® (polatuzumab vedotin-piiq intravenous infusion – Genentech)

REVIEW DATE: 06/28/2023

OVERVIEW

Polivy, a CD79b-directed antibody-drug conjugate, is indicated:[1]

- For the treatment of relapsed or refractory **diffuse large B-cell lymphoma** (DLBCL), not otherwise specified, in combination with bendamustine and a rituximab product in adults after at least two prior therapies.
- For previously untreated **DLBCL**, not otherwise specified or **high-grade B-cell lymphoma**, in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone (R-CHP) in adults with an International Prognostic Index (IPI) score of ≥ 2.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on **B-Cell Lymphomas** (version 4.2023 – June 2, 2023) recommend Polivy for the second-line or subsequent treatment of DLBCL, follicular lymphoma, histologic transformation of indolent lymphoma to DLBCL, AIDS-related B-cell lymphoma, post-transplant lymphoproliferative disorders, and high-grade B-cell lymphoma.[2,3] In addition, NCCN recommends Polivy for the first-line treatment of DLBCL in combination with R-CHP for patients with IPI ≥ 2.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Polivy. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Polivy as well as the monitoring required for adverse events and long-term efficacy, approval requires Polivy to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Polivy is recommended in those who meet one of the following:

FDA-Approved Indications

46. Diffuse Large B-Cell Lymphoma. Approve for 6 months if the patient meets the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following (i or ii):
  - **i.** Patient meets BOTH of the following (a and b):
    - **a)** Patient has an International Prognostic Index score of ≥ 2; AND
    - **b)** Polivy is used as first-line therapy; OR
  - **ii.** Patient has been treated with at least one prior chemotherapy regimen; AND

Note: Examples of chemotherapy regimens include RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) plus rituximab.

C) Polivy is prescribed by or in consultation with an oncologist.

47. High-Grade B-Cell Lymphoma. Approve for 6 months if the patient meets the following (A, B, and C):

A) Patient is ≥ 18 years of age; AND

B) Patient meets ONE of the following (i or ii):

i. Patient meets BOTH of the following (a and b):

a) Patient has an International Prognostic Index score of ≥ 2; AND

b) Polivy is used as first-line therapy; OR

ii. Patient has been treated with at least one prior chemotherapy regimen; AND
Note: Examples of chemotherapy regimens include RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) plus rituximab.

C) Polivy is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

48. B-Cell Lymphoma. Approve for 6 months if the patient meets the following (A, B, and C):
Note: Examples include follicular lymphoma, AIDS-related B-cell lymphoma, post-transplant lymphoproliferative disorders, histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma.

A) Patient is ≥ 18 years of age; AND

B) Patient has been treated with at least one prior chemotherapy regimen; AND
Note: Examples of chemotherapy regimens include CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) plus rituximab or Gazyva (obinutuzumab intravenous infusion), CVP (cyclophosphamide, vincristine, prednisone) plus rituximab or Gazyva, or lenalidomide plus rituximab.

C) Polivy is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Polivy is not recommended in the following situations:

316. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1000. Polivy™ intravenous infusion [prescribing information]. South San Francisco, CA: Genentech; April 2023.

1001. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 4.2023 – June 2, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 23, 2023.

1002. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 23, 2023. Search term: polatuzumab.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Portrazza Prior Authorization Policy
- Portrazza® (necitumumab intravenous infusion – Eli Lilly)

REVIEW DATE: 01/25/2023

OVERVIEW

- Portrazza is indicated in combination with gemcitabine and cisplatin for the first-line treatment of patients with **metastatic squamous non-small cell lung cancer** (NSCLC).[1] It has a limitation of use noted that it is not indicated for the treatment of non-squamous NSCLC.

VVVV)

Guidelines

The National Comprehensive Cancer Network (NCCN) NSCLC cancer guidelines (version 6.2022 – December 2, 2022) no longer address Portrazza in the treatment algorithms. In the discussion section, it is noted that the NCCN Panel feels the addition of Portrazza to gemcitabine and cisplatin is not beneficial based on toxicity, cost, and limited improvement in efficacy when compared with cisplatin/gemcitabine alone.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Portrazza. Because of the specialized skills required for evaluation and diagnosis of patients treated with Portrazza as well as the monitoring required for adverse events and long-term efficacy, approval requires the medication to be prescribed by or in consultation with a prescriber who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Portrazza is recommended in those who meet the following criteria:

FDA-Approved Indication

46. Non-Small Cell Lung Cancer (NSCLC). Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) Patient has metastatic squamous NSCLC; AND

B) Portrazza will be used in combination with chemotherapy; AND

WWWW) Note: Examples of chemotherapy are gemcitabine, cisplatin.

C) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Portrazza is not recommended in the following situations:

142. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

286. Portrazza® intravenous infusion [prescribing information]. Indianapolis, IN: Eli Lilly; November 2015.
287. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 6.2022 – December 2, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 17, 2023.
XXXX)
YYYY)

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Poteligeo Prior Authorization Policy
- Poteligeo® (mogamulizumab-kpkc intravenous infusion – Kyowa Kirin)

REVIEW DATE: 09/06/2023

OVERVIEW
Poteligeo is indicated for the treatment of adult patients with relapsed or refractory **mycosis fungoides** or **Sézary syndrome** after at least one prior systemic therapy.[1]

GUIDELINES
Poteligeo is addressed in the National Comprehensive Cancer Network (NCCN) guidelines:
- **Primary Cutaneous Lymphomas:** Guidelines (version 1.2023 – January 5, 2023) recommend Poteligeo for primary treatment and for treatment of relapsed/refractory mycosis fungoides/Sezary syndrome.[2,3]
- **T-Cell Lymphomas:** Guidelines (version 1.2023 – January 5, 2023) recommend Poteligeo as a single agent for the treatment of relapsed/refractory adult T-cell leukemia/lymphoma, acute or lymphoma subtypes.[3,4]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Poteligeo. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Poteligeo as well as the monitoring required for adverse events and long-term efficacy, approval requires Poteligeo to be prescribed by, or in consultation with, a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Poteligeo is recommended in those who meet one of the following criteria:

FDA-Approved Indication

69. Mycosis Fungoides/Sezary Syndrome. Approve for 1 year if Poteligeo is prescribed by or in consultation with an oncologist or dermatologist.

Other Uses With Supportive Evidence

70. Adult T-cell Leukemia/Lymphoma. Approve for 1 year if the patient meets BOTH of the following (A and B):
- **A)** Patient has relapsed or refractory disease; AND
- **B)** Poteligeo is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Poteligeo is not recommended in the following situations:

143. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

455. Poteligeo® injection [prescribing information]. Bedminster, NJ: Kyowa Kirin; March 2022.
456. NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 1, 2023.
457. NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 1, 2023. Search terms: mogamulizumab-kpkc.
458. NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 1, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Pralatrexate Products Prior Authorization Policy
- Folotyn® (pralatrexate intravenous infusion – Spectrum, generic)

REVIEW DATE: 05/31/2023

OVERVIEW

Folotyn, a dihydrofolate reductase inhibitor, is indicated for the treatment of relapsed or refractory **peripheral T-cell lymphoma**.[1] This indication is based on overall response rate. Continued approval for this indication may be contingent on verification and description of clinical benefit in a confirmatory trial.

Guidelines

Pralatexate is addressed in National Comprehensive Cancer Network (NCCN) guidelines:

- **Primary Cutaneous Lymphomas:** The NCCN clinical practice guidelines (version 1.2023 – January 5, 2023) recommend pralatrexate as systemic therapy for mycosis fungoides/Sezary syndrome with or without skin-directed therapy and as a single agent for primary cutaneous CD30+ T-cell lymphoproliferative disorders.[2,3]
- **T-Cell Lymphomas:** The NCCN clinical practice guidelines (version 1.2023 – January 5, 2023) recommend pralatrexate as a single agent for the second-line or subsequent therapy of relapsed or refractory peripheral T-cell lymphomas including anaplastic large cell lymphoma, peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma, enteropathy-associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, and nodal peripheral T-cell lymphoma with T-follicular helper phenotype; breast implant-associated anaplastic large cell lymphoma; adult T-cell leukemia/lymphoma; extranodal NK/T-cell lymphoma; and hepatosplenic T-cell lymphoma.[3,4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of pralatrexate. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with pralatrexate as well as the monitoring required for adverse events and long-term efficacy, approval requires pralatrexate to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of pralatrexate is recommended in those who meet one of the following criteria:

FDA-Approved Indication

49. T-Cell Lymphoma. Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, D, and E):
Note: Examples of peripheral T-cell lymphoma include anaplastic large cell lymphoma, enteropathy-associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, angioimmunoblastic T-cell lymphoma, peripheral T-cell lymphoma not otherwise specified.

A) Patient is ≥ 18 years of age; AND
B) Patient has peripheral disease; AND
C) Patient has relapsed or refractory disease; AND
D) The medication is used as a single agent; AND
E) The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

50. Adult T-Cell Leukemia/Lymphoma. Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has acute or lymphoma subtype; AND
C) The medication is used as second-line or subsequent therapy; AND
D) The medication is used as a single agent; AND
E) The medication is prescribed by or in consultation with an oncologist.

51. Breast Implant-Associated Anaplastic Large Cell Lymphoma. Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has relapsed or refractory disease; AND
C) The medication is used as a single agent; AND
D) The medication is prescribed by or in consultation with an oncologist.

52. Cutaneous CD30+ T-Cell Lymphoproliferative Disorders. Approve for 1 year if the patient meets All of the following criteria (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has one of the following diagnoses (i or ii):
i. Primary cutaneous anaplastic large cell lymphoma with multifocal lesions; OR
ii. Cutaneous anaplastic large cell lymphoma with regional nodes; AND
C) The medication is used as a single agent; AND
D) The medication is prescribed by or in consultation with an oncologist.

53. Extranodal NK/T-Cell Lymphoma. Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has relapsed/refractory disease following combination, asparaginase-based chemotherapy; AND
C) The medication is used as a single agent; AND
D) The medication is prescribed by or in consultation with an oncologist.

54. Hepatosplenic T-Cell Lymphoma. Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) The medication is used as second-line or subsequent therapy; AND
C) The medication is used as a single agent; AND
D) The medication is prescribed by or in consultation with an oncologist.

55. Mycosis Fungoides/Sezary Syndrome. Approve for 1 year if the patient meets BOTH of the following criteria (A and B):
A) Patient is ≥ 18 years of age; AND

B) The medication is prescribed by or in consultation with an oncologist or dermatologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of pralatrexate is not recommended in the following situations:

317. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1003. Folotyn® injection [prescribing information]. East Windsor, NJ: Acrotech Biopharma; October 2020.
1004. The NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 15, 2023.
1005. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 15, 2023. Search term: pralatrexate.
1006. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 15, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Proleukin Prior Authorization Policy
- Proleukin® (aldesleukin intravenous infusion – Prometheus Laboratories)

REVIEW DATE: 01/18/2023

OVERVIEW

Proleukin, a human recombinant interleukin-2 product, is indicated for the following conditions, in adults:
- **Metastatic melanoma**.
- **Metastatic renal cell carcinoma**.[1]

Guidelines

Proleukin is addressed in the following National Comprehensive Cancer Network guidelines:
- **Cutaneous melanoma** (version 1.2023 – December 22, 2022) clinical practice guidelines recommend Proleukin for unresectable or metastatic disease as a single agent for second-line or subsequent therapy for disease progression or after maximum clinical benefit from BRAF targeted therapy (category 2A).[2,4] Proleukin may be considered for patients with small brain tumors and without significant peritumoral edema (category 2B) or for intralesional therapy as primary or second-line treatment of unresectable stage III disease with clinical or satellite/in-transit metastases, or local satellite/in-transit recurrence (category 2B).
- **Hematopoietic cell transplantation** (version 2.2022 – September 28, 2022) clinical practice guidelines recommend Proleukin as additional therapy, in combination with systemic corticosteroids, for steroid-refractory chronic graft-vs-host disease.[2,5]
- **Kidney cancer** (version 3.2023 – September 22, 2022) clinical practice guidelines recommend Proleukin as a single agent for first-line (category 2B) and subsequent (category 2B) therapy for patients with relapsed or stage IV disease and clear cell histology.[2,3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Proleukin. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Proleukin as well as the monitoring required for adverse events and long-term efficacy, approval requires Proleukin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Proleukin is recommended in those who meet one of the following criteria:

FDA-Approved Indications

56. Cutaneous Melanoma. Approve for 1 year if the patient meets ONE of the following (A or B):

A) Intravenous Therapy. Approve if the patient meets the following criteria (i, ii, iii, iv, and v):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has metastatic or unresectable disease; AND

iii. Patient has tried at least one other systemic therapy; AND
iv. Proleukin will be used as a single agent; AND
v. Proleukin is prescribed by or in consultation with an oncologist.

B) Intralesional Therapy. Approve if the patient meets the following criteria (i, ii, and iii):
i. Patient is ≥ 18 years of age; AND
ii. Proleukin will be directly injected into metastatic, recurrent, or unresectable cutaneous, subcutaneous, or nodal lesions; AND
iii. The medication is prescribed by or in consultation with an oncologist or dermatologist.

57. Kidney Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has relapsed or metastatic disease; AND
C) Patient has clear cell histology; AND
D) Proleukin will be used as a single agent; AND
E) Proleukin is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

58. Graft-Versus-Host Disease. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
A) Patient has chronic graft-versus-host disease; AND
B) According to the prescriber, the patient has steroid-refractory disease; AND
C) Proleukin will be used in combination with systemic corticosteroids; AND
D) Proleukin will be prescribed by or in consultation with an oncologist or a physician associated with a transplant center.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Proleukin is not recommended in the following situations:

318. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1007. Proleukin® intravenous infusion [prescribing information]. San Diego, CA: Prometheus Laboratories; September 2019.
1008. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 10, 2023. Search term: aldesleukin.
1009. The NCCN Kidney Cancer Clinical Practice Guidelines (version 3.2023 – September 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed January 10, 2023.
1010. The NCCN Cutaneous Melanoma Clinical Practice Guidelines (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed January 10, 2023.
1011. The NCCN Hematopoietic Cell Transplantation Clinical Practice Guidelines (version 2.2022 – September 28, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed January 10, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Rituxan Hycela Prior Authorization Policy
- Rituxan Hycela® (rituximab and hyaluronidase human subcutaneous injection – Biogen and Genentech/Roche)

REVIEW DATE: 12/21/2022

OVERVIEW

Rituxan Hycela, a combination of rituximab and hyaluronidase human, is indicated for treatment of adults with the following indications:

- **Diffuse large B-cell lymphoma**, in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or other anthracycline-based chemotherapy regimens in patients with previously untreated disease.
- **Chronic lymphocytic leukemia**, in combination with FC (fludarabine + cyclophosphamide) for previously treated and previously untreated disease.
- **Follicular lymphoma**, as a single agent for relapsed or refractory disease; in previously untreated disease in combination with first-line chemotherapy and, as single-agent maintenance therapy in patients achieving a complete or partial response to rituximab + chemotherapy; and as a single agent after first-line CVP (cyclophosphamide, vincristine, and prednisone) in non-progressing (including stable disease) disease.

Rituxan Hycela contains the identical molecular antibody of rituximab available in Rituxan intravenous, but hyaluronidase has been added to facilitate systemic delivery. Rituxan Hycela should be administered under the care of a healthcare professional with appropriate medical support to manage severe and potentially fatal reactions. The dose of Rituxan Hycela is fixed regardless of the patient's body surface area; dose reductions are not recommended. When given in combination with chemotherapy, reduce the dose of chemotherapeutic drugs to manage adverse events. Rituxan Hycela is not indicated for treatment of non-malignant conditions.

Guidelines

Rituximab features prominently in the National Comprehensive Cancer Network (NCCN) guidelines for multiple conditions. The following guidelines from NCCN have been updated to list Rituxan Hycela (noted as rituximab + hyaluronidase) in most clinical scenarios when the intravenous formulation is recommended, if the patient has received the first full dose with rituximab intravenous.

- **B-cell Lymphomas:** In the guidelines (version 5.2022 – July 12, 2022), rituximab is included in multiple treatment regimens across the spectrum of disease.[2] For primary cutaneous B-cell lymphomas (version 2.2022 – June 8, 2022), rituximab is a treatment option for patients with primary cutaneous B-cell lymphoma.[7]
- **Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma:** Rituximab features prominently in the guidelines (version 1.2023 – August 30, 2022) and is included in multiple treatment regimens across the spectrum of disease.[3]
- **Hairy Cell Leukemia:** Guidelines (version 1.2023 – August 30, 2022) recommend rituximab in multiple regimens for relapsed/refractory disease, including in patients with progressive disease after relapsed/refractory therapy.[4]
- **Hodgkin Lymphoma:** Guidelines (version 2.2023 – November 8, 2022) recommend rituximab ± chemotherapy and/or radiation (depending on the clinical presentation) in the first-line setting for

nodular lymphocyte-predominant disease.[8] Rituximab is also used for relapsed/refractory disease and for maintenance.

- **Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma:** Guidelines (version 1.2023 – July 6, 2022) include rituximab in regimens across the spectrum of disease (primary therapy, previously treated disease, and maintenance).[5]

Safety

There is a higher risk of hypersensitivity and other acute reactions during the first infusion.[1] Therefore, all patients must receive at least one full dose of rituximab intravenous, which allows for management by slowing or stopping the infusion, before receiving Rituxan Hycela. Patients who are unable to complete one full intravenous infusion should continue to receive subsequent cycles with Rituxan intravenous and should not switch to Rituxan Hycela until a full intravenous dose is successfully administered. Safety is otherwise comparable to rituximab intravenous.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Rituxan Hycela. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Rituxan Hycela as well as the monitoring required for adverse events and long-term efficacy, approval requires Rituxan Hycela to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rituxan Hycela is recommended in those who meet one of the following criteria:

FDA-Approved Indications

39. B-Cell Lymphoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
86. Note: Examples of B-cell lymphomas include diffuse large B-cell lymphoma [DLBCL], follicular lymphoma, acquired immune deficiency [AIDS]-related B-cell lymphoma, Burkitt lymphoma, Castleman's disease, marginal zone lymphoma [e.g., extranodal or MALT {gastric or nongastric}, nodal, or splenic marginal zone lymphoma], primary mediastinal large B-cell lymphoma, mantle cell lymphoma, post-transplant lymphoproliferative disorders, gray zone lymphoma, primary cutaneous B-cell lymphoma.

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has already received at least one full dose of rituximab intravenous; AND
- **C)** Rituxan Hycela is administered under the care of a healthcare professional; AND
- **D)** The medication is being prescribed by or in consultation with an oncologist.

40. Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has already received at least one full dose of rituximab intravenous; AND
- **C)** Rituxan Hycela is administered under the care of a healthcare professional; AND
- **D)** The medication is being prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

41. **Hairy Cell Leukemia.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
    - **A)** Patient is ≥ 18 years of age; AND
    - **B)** Patient has relapsed/refractory hairy cell leukemia; AND
    - **C)** Patient has already received at least one full dose of rituximab intravenous; AND
    - **D)** Rituxan Hycela is administered under the care of a healthcare professional; AND
    - **E)** The medication is prescribed by or in consultation with an oncologist.

42. **Hodgkin Lymphoma**. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
    - **A)** Patient is ≥ 18 years of age; AND
    - **B)** Patient has nodular lymphocyte-predominant disease; AND
    - **C)** Patient has already received at least one full dose of rituximab intravenous; AND
    - **D)** Rituxan Hycela is administered under the care of a healthcare professional; AND
    - **E)** The medication is prescribed by or in consultation with an oncologist

43. **Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
    - **A)** Patient is ≥ 18 years of age; AND
    - **B)** Patient has already received at least one full dose of rituximab intravenous; AND
    - **C)** Rituxan Hycela is administered under the care of a healthcare professional; AND
    - **D)** The medication is being prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rituxan Hycela is not recommended in the following situations:

144. **Granulomatosis with Polyangiitis (Wegener's granulomatosis) or Microscopic Polyangiitis.** Rituximab intravenous is indicated for treatment of these indications.[6] Rituxan Hycela has not been evaluated and does not have established dosing in this setting.

145. **Pemphigus Vulgaris.** Rituximab intravenous is indicated for treatment of pemphigus vulgaris.[6] Rituxan Hycela has not been evaluated and does not have established dosing for pemphigus vulgaris.

146. **Rheumatoid Arthritis.** Rituximab intravenous is indicated for treatment of rheumatoid arthritis.[6] Rituxan Hycela has not been evaluated and does not have established dosing for rheumatoid arthritis.

147. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

223. Rituxan Hycela® subcutaneous injection [prescribing information]. South San Francisco, CA: Biogen and Genentech/Roche; June 2021.
224. The NCCN B-Cell Lymphoma Clinical Practice Guidelines in Oncology (version 5.2022 – July 12, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 13, 2022.
225. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (version 1.2023 – August 30, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on August 30, 2022.

226. The NCCN Hairy Cell Leukemia Clinical Practice Guidelines in Oncology (version 1.2023 – August 30, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 13, 2022.
227. The NCCN Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma Clinical Practice Guidelines in Oncology (version 1.2023 – July 6, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 13, 2022.
228. Rituxan® intravenous infusion [prescribing information]. South San Francisco, CA: Biogen and Genentech/Roche; June 2021.
229. The NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (version 2.2022 – June 8, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 13, 2022.
230. The NCCN Hodgkin Lymphoma Clinical Practice Guidelines in Oncology (version 2.2023 – November 8, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 13, 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Romidepsin Products Prior Authorization Policy
- Istodax® (romidepsin intravenous infusion – Celegene, generics)

REVIEW DATE: 06/14/2023

OVERVIEW

Romidepsin, a histone deacetylase inhibitor, is indicated for the treatment of **cutaneous T-cell lymphoma** in patients who have received at least one prior systemic therapy.[1]

Guidelines

Romidepsin is addressed in National Comprehensive Cancer Network (NCCN) guidelines:

- **Primary Cutaneous Lymphomas:** Guidelines (version 1.2023 – January 5, 2023) recommend romidepsin as systemic therapy for mycosis fungoides/Sezary syndrome with or without skin-directed therapy and as a single agent for relapsed or refractory primary cutaneous CD30+ T-cell lymphoproliferative disorders.[2,3]
- **T-Cell Lymphomas:** Guidelines (version 1.2023 – January 5, 2023) recommend romidepsin as a single agent for the second-line or subsequent therapy of relapsed or refractory peripheral T-cell lymphomas including anaplastic large cell lymphoma; peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma, enteropathy-associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, and nodal peripheral T-cell lymphoma with T-follicular helper (TFH) phenotype; follicular T-cell lymphoma; breast implant-associated anaplastic large cell lymphoma; extranodal NK/T-cell lymphoma; and hepatosplenic T-cell lymphoma.[3,4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of romidepsin. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with romidepsin as well as the monitoring required for adverse events and long-term efficacy, approval requires romidepsin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of romidepsin is recommended in those who meet one of the following criteria:

FDA-Approved Indications

59. Cutaneous CD30+ T-Cell Lymphoproliferative Disorders. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has relapsed or refractory disease; AND
- **C)** Patient has one of the following diagnoses (i or ii):
  - **i.** Primary cutaneous anaplastic large cell lymphoma with multifocal lesions; OR

ii. Cutaneous anaplastic large cell lymphoma with regional nodes; AND

D) Romidepsin is used as a single agent; AND

E) Romidepsin is prescribed by or in consultation with an oncologist.

60. Mycosis Fungoides/Sezary Syndrome. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient is ≥ 18 years of age; AND

B) The medication is prescribed by or in consultation with an oncologist or dermatologist.

Other Uses with Supportive Evidence

61. Breast Implant-Associated Anaplastic Large Cell Lymphoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient has relapsed or refractory disease; AND

C) Romidepsin is used as a single agent; AND

D) Romidepsin is prescribed by or in consultation with an oncologist.

62. Extranodal NK/T-Cell Lymphoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient has relapsed/refractory disease following combination asparaginase-based chemotherapy; AND

Note: Examples of asparaginase-based chemotherapy include modified SMILE (steroid [dexamethasone], methotrexate, ifosfamide, pegaspargase, and etoposide), P-GEMOX (gemcitabine, pegaspargase, and oxaliplatin), and DDGP (dexamethasone, cisplatin, gemcitabine, pegaspargase).

C) Romidepsin is used as a single agent; AND

D) Romidepsin is prescribed by or in consultation with an oncologist.

63. Hepatosplenic T-Cell Lymphoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Romidepsin is used as subsequent therapy after two primary treatment regimens; AND

Note: Examples of primary treatment regimens include ICE (ifosfamide, carboplatin, etoposide), DHAP (dexamethasone, cytarabine, cisplatin), DHAX (dexamethasone, cytarabine, oxaliplatin), IVAC (ifosfamide, etoposide, cytarabine).

C) Romidepsin is used as a single agent; AND

D) Romidepsin is prescribed by or in consultation with an oncologist.

64. T-Cell Lymphoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):

Note: Examples of peripheral T-cell lymphoma include anaplastic large cell lymphoma, enteropathy-associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, angioimmunoblastic T-cell lymphoma, peripheral T-cell lymphoma not otherwise specified.

A) Patient is ≥ 18 years of age; AND

B) Patient has peripheral disease; AND

C) Patient has relapsed or refractory disease; AND

D) Romidepsin is used as a single agent; AND

E) Romidepsin is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of romidepsin is not recommended in the following situations:

319. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1012. Istodax® intravenous infusion [prescribing information]. Summit, NJ: Celgene; July 2021.

1013. The NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 6, 2023.

1014. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 6, 2023. Search term: romidepsin.

1015. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 6, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Rybrevant Prior Authorization Policy
- Rybrevant™ (amivantamab-vmjw intravenous infusion – Janssen)

REVIEW DATE: 06/14/2023

OVERVIEW

Rybrevant, a bispecific epidermal growth factor receptor (EGFR)-directed and mesenchymal epithelial transition (MET) receptor-directed antibody, is indicated for the treatment of locally advanced or metastatic **non-small cell lung cancer** with EGFR exon 20 insertion mutations, in adults, as detected by a FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.[1] This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Guidelines

The National Comprehensive Cancer Network (NCCN) non-small cell lung cancer guidelines (version 3.2023 – April 13, 2023) recommend Rybrevant for the subsequent treatment of EGFR exon 20 insertion mutation positive recurrent, advanced, or metastatic non-small cell lung cancer as a single agent.[2,3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Rybrevant. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Rybrevant as well as the monitoring required for adverse events and long-term efficacy, approval requires Rybrevant to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rybrevant is recommended in those who meet the following criteria:

FDA-Approved Indication

65. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has epidermal growth factor receptor exon 20 insertion mutations, as detected by an approved test; AND
- **C)** The medication is used as subsequent therapy; AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rybrevant is not recommended in the following situations:

320. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1016. Rybrevant intravenous infusion [prescribing information]. Horsham, PA: Janssen; November 2021.
1017. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 9, 2023. Search term: amivantamab.
1018. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – April 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 9, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Rylaze Prior Authorization Policy
- Rylaze™ (asparaginase erwinia chrysanthemi [recombinant]-rywn intramuscular injection – Jazz)

REVIEW DATE: 06/28/2023

OVERVIEW

Rylaze, asparaginase erwinia chrysanthemi (recombinant), is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of **acute lymphoblastic leukemia** (ALL) and **lymphoblastic lymphoma** (LBL) in adults and pediatric patients ≥ 1 month who have developed hypersensitivity to *E. coli*-derived asparaginase.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) has addressed Rylaze:

- **ALL** (version 1.2023 – May 31, 2023) and **Pediatric ALL** (version 2.2023 – March 10, 2023) guidelines recommend Rylaze for patients who develop a systemic allergic reaction or anaphylaxis to pegaspargase.[2-4]
- **T-Cell Lymphomas:** NCCN guidelines (version 1.2023 – January 5, 2023) recommend Rylaze for patients with extranodal NK/T-Cell lymphoma who develop a systemic allergic reaction or anaphylaxis to pegaspargase.[2,5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Rylaze. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Rylaze as well as the monitoring required for adverse events and long-term efficacy, approval requires Rylaze to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rylaze is recommended in those who meet the following:

FDA-Approved Indication

66. Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma. Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient has a systemic allergic reaction or anaphylaxis to a pegylated asparaginase product; AND
- **B)** Rylaze is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

67. Extranodal NK/T-Cell Lymphoma. Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient has a systemic allergic reaction or anaphylaxis to a pegylated asparaginase product; AND

B) Rylaze is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rylaze is not recommended in the following situations:

321. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1019. Rylaze intramuscular injection [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals; November 2022.

1020. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 23, 2023. Search term: asparaginase erwinia chrysanthemi (recombinant)-rywn.

1021. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 1.2023 – May 31, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 23, 2023.

1022. The NCCN Pediatric Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 2.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 23, 2023.

1023. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 23, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Sarclisa Prior Authorization Policy
- Sarclisa® (isatuximab-irfc intravenous infusion – Sanofi-Aventis)

REVIEW DATE: 04/12/2023

OVERVIEW

Sarclisa, a CD38-directed monoclonal antibody, is indicated in adults with **multiple myeloma**, in the following situations:[1]

- in combination with Pomalyst® (pomalidomide capsules) and dexamethasone in patients who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor.
- in combination with Kyprolis® (carilzomib intravenous infusion) and dexamethasone in patients with relapsed or refractory disease who have received one to three prior lines of therapy.

Guidelines

Guidelines from the National Comprehensive Cancer Network (NCCN) [version 3.2023 – December 8, 2022] include Sarclisa/Kyprolis/dexamethasone and Sarclisa/Pomalyst/dexamethasone (after two prior therapies, including lenalidomide and a proteasome inhibitor) among the preferred regimens (both combinations are category 1) for previously treated multiple myeloma, for early relapses (one to three prior therapies) in bortezomib- and lenalidomide-refractory disease.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Sarclisa. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sarclisa as well as the monitoring required for adverse events and long-term efficacy, approval requires Sarclisa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sarclisa is recommended in those who meet the following criteria:

FDA-Approved Indication

44. Multiple Myeloma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **47.** Patient is ≥ 18 years of age; AND
- **48.** Patient meets one of the following (i or ii):
- **A)** All of the following apply (a, b, c, and d):
  - **a)** The medication will be used in combination with Pomalyst (pomalidomide capsules) and dexamethasone; AND
  - **b)** Patient has tried at least TWO prior regimens for multiple myeloma; AND
    Note: Examples include bortezomib/lenalidomide/dexamethasone, Kyprolis (carfilzomib intravenous infusion)/lenalidomide/dexamethasone, Darzalex (daratumumab intravenous

infusion)/bortezomib/melphalan/prednisone, Ninlaro (ixazomib capsules)/lenalidomide/dexamethasone, and Darzalex/lenalidomide/dexamethasone.

c) A proteasome inhibitor was a component of at least one previous regimen; AND
Note: Examples of proteasome inhibitors include bortezomib, Kyprolis, Ninlaro.

d) Lenalidomide was a component of at least one previous regimen; OR

B) Patient meets both of the following (a and b):

i. The medication will be used in combination with Kyprolis and dexamethasone; AND

ii. Patient has tried at least ONE prior regimen; AND

49. The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sarclisa is not recommended in the following situations:

322. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

53. Sarclisa® intravenous infusion [prescribing information]. Bridgewater, NJ: Sanofi-Aventis; July 2022.
54. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 10, 2023. Search term: isatuximab.
55. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 3.2023 – December 8, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 10, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Sylvant Prior Authorization Policy
- Sylvant® (siltuximab intravenous infusion – EUSA Pharma)

REVIEW DATE: 01/18/2023

OVERVIEW

Sylvant, an interleukin (IL)-6 antagonist, is indicated for treatment of patients with **multicentric Castleman's disease** (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative.[1] Because Sylvant did not bind to virally produced IL-6 in a nonclinical study, Sylvant has not been studied in patients with MCD who are HIV positive or HHV-8 positive. The pivotal trials showed a higher proportion of patients with durable tumor response (partial or complete response) and improvement in patient-reported outcomes (e.g., fatigue, physical function) with Sylvant vs. placebo. Patients were treated until treatment failure, defined as disease progression based on increased symptoms, radiologic progression, or deterioration in performance status. Safety and efficacy has not been established in patients < 18 years of age.

Disease Overview

MCD affects approximately 1,000 patients in the US. It typically presents with lymphoid hyperplasia at multiple sites, including the peripheral lymph nodes, bone marrow, and multiple organs. Patients often have serious infections, fevers, weight loss, fatigue, night sweats, and nerve damage that can cause weakness and numbness. Persistent IL-6 production has been implicated in the development of various autoimmune, chronic, inflammatory diseases and cancers, including MCD.[2] Sylvant, a human-mouse chimeric monoclonal antibody that is produced by Chinese hamster ovary cells, binds human IL-6 and prevents the binding of IL-6 to both soluble and membrane-bound IL-6 receptors.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for B-cell lymphomas (version 5.2022 – July 12, 2022) list Sylvant as a treatment option for MCD and for refractory or relapsed unicentric disease.[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Sylvant. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sylvant as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Sylvant to be prescribed by or in consultation with a physician who specializes in the condition being treated.

All reviews for use of Sylvant for COVID-19 and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sylvant is recommended in those who meet the following criteria:

FDA-Approved Indication

H) Castleman's Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

G) Initial Therapy. Approve for 6 months if the patient meets ALL of the following conditions (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Patient is negative for the human immunodeficiency virus (HIV) and human herpesvirus-8 (HHV-8); AND

iii. Patient meets ONE of the following (a or b):

a) Patient has multicentric Castleman's disease; OR

b) Sylvant is being used for relapsed or refractory unicentric Castleman's disease; AND

iv. Sylvant is prescribed by or in consultation with an oncologist or hematologist.

B) Patient is Currently Receiving Sylvant. Approve for 1 year if the patient meets both of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate, fibrinogen, albumin, and/or hemoglobin), increased body mass index, and/or reduction in lymphadenopathy.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as improvement or resolution of constitutional symptoms (e.g., fatigue, physical function).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sylvant is not recommended in the following situations:

1. **COVID-19 (Coronavirus Disease 2019).** Forward all requests to the Medical Director.
Note: This includes requests for cytokine release syndrome associated with COVID-19.

2. Multiple Myeloma. Efficacy is not established. In a Phase II study (n = 286) evaluating patients with relapsed or refractory multiple myeloma, median progression-free survival was similar in patients treated with Velcade (bortezomib injection) + Sylvant (8.0 months) vs. in those treated with Velcade + placebo (7.6 months).[4] Following 24.5 months of follow-up, there was not a significant difference between the groups in median overall survival (30.8 months in the group that received Velcade + Sylvant vs. 36.8 months in the Velcade + placebo group). There was not a significant difference in overall response rate or other secondary endpoints. Another Phase II study evaluated Sylvant in patients (n = 106) with previously untreated symptomatic multiple myeloma who were transplant-ineligible.[6] There was not a significant difference in complete response rate or overall response rate in patients treated with Velcade/melphalan/prednisone (VMP) vs. those treated with VMP + Sylvant. Progression-free survival and overall survival

was the same in the two treatment groups. Another Phase II study in adults with relapsed or refractory multiple myeloma did not show any response with Sylvant monotherapy compared with 8% response rate in those who received Sylvant + dexamethasone.[7]

3. **Myelodysplastic Syndrome (MDS).** Efficacy is not established. A double-blind, placebo-controlled, Phase II study assigned adults with MDS (n = 76) to treatment with best supportive care in combination with Sylvant or placebo.[5] There was not a significant difference in the proportion of patients with reduced transfusions to treat anemia (primary endpoint). The study was terminated early due to lack of efficacy.

4. **Prostate Cancer.** Efficacy is not established. An open-label Phase II study did not demonstrate added efficacy with Sylvant added on to mitoxantrone/prednisone vs. mitoxantrone/prednisone.[8] Although the treatment groups were not balanced, progression-free survival was 97 days in the group that received Sylvant/mitoxantrone/prednisone vs. 228 days with mitoxantrone/prednisone. The study was stopped early.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1024. Sylvant® intravenous infusion [prescribing information]. Hemel Hempstead, Hertfordshire, UK: EUSA Pharma; April 2022.
1025. Tanaka T, Kishimoto T. Targeting interleukin-6: all the way to treat autoimmune and inflammatory diseases. *Int J Biol Sci*. 2012;8(9):1227-1236.
1026. The NCCN B-Cell Lymphoma Clinical Practice Guidelines in Oncology (version 5.2022 – July 12, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 17, 2023.
1027. Orlowski RZ, Gercheva L, Williams C, et al. A phase 2, randomized, double-blind, placebo-controlled study of siltuximab (anti-IL-6 mAb) and bortezomib versus bortezomib alone in patients with relapsed or refractory multiple myeloma. *Am J Hematol*. 2015;90(1):42-49.
1028. Garcia-Manero G, Gartenberg G, Steensma DP, et al. A phase 2, randomized, double-blind, multicenter study comparing siltuximab plus best supportive care (BSC) with placebo plus BSC in anemic patients with International Prognostic Scoring System low- or intermediate-1-risk myelodysplastic syndrome. *Am J Hematol*. 2014;89(9):E156-62.
1029. San-Miguel J, Bladé J, Shpilberg O, et al. Phase 2 randomized study of bortezomib-melphalan-prednisone with or without siltuximab (anti-IL-6) in multiple myeloma. *Blood*. 2014;123(26):4136-4142.
1030. Voorhees PM, Manges RF, Sonneveld P, et al. A phase 2 multicentre study of siltuximab, an anti-interleukin-6 monoclonal antibody, in patients with relapsed or refractory multiple myeloma. *Br J Haematol*. 2013;161(3):357-366.
1031. Fizazi K, De Bono JS, Flechon A, et al. Randomised phase II study of siltuximab (CNTO 328), an anti-IL-6 monoclonal antibody, in combination with mitoxantrone/prednisone versus mitoxantrone/prednisone alone in metastatic castration-resistant prostate cancer. *Eur J Cancer*. 2012;48(1):85-93.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Synribo Prior Authorization Policy
- Synribo® (omacetaxine mepesuccinate subcutaneous injection – Teva)

REVIEW DATE: 10/11/2023

OVERVIEW

Synribo is indicated for the treatment of **chronic or accelerated phase chronic myeloid leukemia** (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKIs) in adults.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for **CML** (version 1.2024 – August 1, 2023) recommend Synribo as a treatment option for patients with resistance and/or intolerance to two or more TKIs with chronic phase CML that is Philadelphia chromosome or breakpoint cluster gene – Abelson proto-oncogene (BCR-ABL1) positive; as treatment of advanced phase CML for patients with disease progression to accelerated phase CML; and post-allogenic hematopoietic stem cell transplant follow-up therapy.[2] It is not an option among patients who present with accelerated phase CML. Synribo is also a treatment option for patients with the T315I mutation.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Synribo. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Synribo as well as the monitoring required for adverse events and long-term efficacy, approval requires Synribo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Synribo is recommended in those who meet the following criteria:

FDA-Approved Indication

68. Chronic Myeloid Leukemia. Approve for 6 months if the patient meets the following (A, B, C and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has Philadelphia chromosome-positive chronic myeloid leukemia (CML); AND
- **C)** Patient meets one of the following (i or ii):
  - **i.** Patient is T315I-positive; OR
  - **ii.** Patient has tried at least two tyrosine kinase inhibitors indicated for use in CML; AND
    Note: Examples include imatinib tablets, Sprycel (dasatinib tablets), Tasigna (nilotinib capsules), Bosulif (bosutinib tablets), and Iclusig (ponatinib tablets).

Medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Synribo is not recommended in the following situations:

323. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

56. Synribo® subcutaneous injection [prescribing information]. North Wales, PS: Teva; May 2021.
57. The NCCN Chronic Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 1.2024 – August 1, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 6, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Talvey Prior Authorization Policy
- Talvey™ (talquetamab-tgvs subcutaneous injection – Janssen Biotech)

REVIEW DATE: 08/16/2023

OVERVIEW

Talvey, a bispecific GPRC5D-directed CD3 T-cell engager, is indicated for the treatment of relapsed or refractory **multiple myeloma** in adults who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.[1]

Guidelines

Guidelines have not yet addressed Talvey. For late relapse or progressive multiple myeloma in patients who have received at least four previous therapies including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody, the National Comprehensive Cancer Network (NCCN) **multiple myeloma** (version 3.2023 – December 8, 2022) clinical practice guidelines recommend Abecma® (idecabtagene vicleucel intravenous [IV] infusion), Carvykti™ [ciltacabtagene autoleucel IV infusion]), or Tecvayli™ (teclistamab-cqyv subcutaneous injection).[2] Blenrep™ (belantamab mafodotin-blmf IV infusion) is listed as "Useful in Certain Circumstances".

Safety

Talvey was approved with a Risk Evaluation and Mitigation Strategy (REMS) program due to the risk of cytokine release syndrome and neurotoxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS).[1]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Talvey. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Talvey as well as the monitoring required for adverse events and long-term efficacy, approval requires Talvey to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Talvey is recommended in those who meet the following criteria:

FDA-Approved Indication

45. Multiple Myeloma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
- **50.** Patient is ≥ 18 years of age; AND
- **51.** Patient has tried at least four systemic regimens; AND
- **52.** Among the previous regimens tried, the patient has received at least one drug from each of the following classes (i, ii, and iii):
- **iv.** Proteasome inhibitor; AND

Note: Examples include bortezomib, Kyprolis (carfilzomib intravenous infusion), Ninlaro (ixazomib capsules).

v. Immunomodulatory drug; AND
Note: Examples include lenalidomide, Pomalyst (pomalidomide capsules), Thalomid (thalidomide capsules).

vi. Anti-CD38 monoclonal antibody; AND
Note: Examples include Darzalex (daratumumab intravenous infusion), Darzalex Faspro (daratumumab and hyaluronidase-fihj subcutaneous injection), or Sarclisa (isatuximab-irfc intravenous infusion).

D) The medication will be prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Talvey is not recommended in the following situations:

324. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1032. Talvey™ subcutaneous injection [prescribing information]. Horsham, PA: Janssen Biotech.; August 2023.
1033. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 2.2023 – December 8, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on August 10, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Tecvayli Prior Authorization Policy
- Tecvayli™ (teclistamab-cqyv subcutaneous injection – Janssen Biotech)

REVIEW DATE: 11/08/2023

OVERVIEW
Tecvayli, a bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager, is indicated for the treatment of adults with relapsed or refractory **multiple myeloma** who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.[1]

Guidelines
The National Comprehensive Cancer Network (NCCN) multiple myeloma (version 2.2024 – November 1, 2023) clinical practice guidelines recommend Tecvayli for relapsed or refractory disease in patients who have received at least four previous therapies including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.[2,3]

Safety
Tecvayli was approved with a Risk Evaluation and Mitigation Strategy (REMS) program due to the risk of cytokine release syndrome and neurotoxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS).[1]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Tecvayli. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tecvayli as well as the monitoring required for adverse events and long-term efficacy, approval requires Tecvayli to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Tecvayli is recommended in those who meet the following criteria:

FDA-Approved Indication

46. Multiple Myeloma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
- **53.** Patient is ≥ 18 years of age; AND
- **54.** Patient has tried at least four systemic regimens; AND
- **55.** Among the previous regimens tried, the patient has received at least one drug from each of the following classes (i, ii, and iii):
- **vii.** Proteasome inhibitor; AND
  87. Note: Examples include bortezomib, Kyprolis (carfilzomib intravenous infusion), Ninlaro (ixazomib capsules).

viii. Immunomodulatory drug; AND

88. Note: Examples include lenalidomide, Pomalyst (pomalidomide capsules), Thalomid (thalidomide capsules).

ix. Anti-CD38 monoclonal antibody; AND

89. Note: Examples include Darzalex (daratumumab intravenous infusion), Darzalex Faspro (daratumumab and hyaluronidase-fihj subcutaneous injection), or Sarclisa (isatuximab-irfc intravenous infusion).

E) The medication will be prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tecvayli is not recommended in the following situations:

325. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1034. Tecvayli™ subcutaneous injection [prescribing information]. Horsham, PA: Janssen Biotech.; August 2023.

1035. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 6, 2023. Search term: teclistamab.

1036. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 2.2024 – November 1, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 6, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Thiotepa Products Prior Authorization Policy
- Tepadina® (thiotepa intravenous, intracavitary, or intravesical injection – Adienne, generic)

REVIEW DATE: 12/13/2023

OVERVIEW

Thiotepa is an alkylating agent indicated for:
- **Beta-thalassemia**, to reduce the risk of graft rejection when used in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogeneic hematopoietic progenitor (stem) cell transplantation for pediatric patients with class 3 disease.[1]
- **Bladder cancer**, for superficial papillary carcinoma of the urinary bladder.[1,2]
- **Breast adenocarcinoma**.[1,2]
- **Neoplastic diseases of various serosal cavities**, for controlling intracavitary effusions secondary to diffuse or localized disease.[1,2]
- **Ovarian adenocarcinoma**.[1,2]

Guidelines

Thiotepa is addressed in National Comprehensive Cancer Network (NCCN) guidelines:
- **Bladder cancer:** Guidelines (version 3.2023 – May 25, 2023) state that intravesical thiotepa does not appear to be effective. NCCN recommends gemcitabine and mitomycin for intravesical chemotherapy.[5]
- **Breast cancer:** Guidelines (version 5.2023 – December 5, 2023) do not provide any recommendations on the use of thiotepa in the management of breast cancer.[3]
- **Central nervous system (CNS) cancers:** Guidelines (version 1.2023 – March 24, 2023) recommend thiotepa, in combination with methotrexate, cytarabine, and rituximab for induction therapy, in combination with other chemotherapy agents for relapsed or refractory disease, or in combination with carmustine or busulfan and cyclophosphamide, with stem cell rescue for consolidation therapy of primary CNS lymphoma.[6] NCCN recommends intra-cerebrospinal fluid thiotepa for the treatment of leptomeningeal metastases.
- **Hematopoietic Cell Transplantation:** Guidelines (version 3.2023 – October 9, 2023) recommend thiotepa as a component of a variety of conditioning regimens for autologous, allogeneic, and umbilical cord blood transplants.[7,8]
- **Ovarian cancer:** Guidelines (version 2.2023 – June 2, 2023) do not provide any recommendations on the use of thiotepa in the management of ovarian cancer.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of thiotepa. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with thiotepa as well as the monitoring required for adverse events and long-term efficacy, approval requires thiotepa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of thiotepa is recommended in those who meet one of the following criteria:

FDA-Approved Indications

69. Beta-Thalassemia. Approve for 1 month if the patient meets ALL of the following (A, B, C, D, and E):
- **A)** Patient is ≤ 18 years of age; AND
- **B)** Patient has class 3 beta-thalassemia; AND
- **C)** Thiotepa will be used prior to allogeneic hematopoietic stem cell transplantation; AND
- **D)** Thiotepa will be used in combination with high-dose busulfan and cyclophosphamide; AND
- **E)** The medication is prescribed by or in consultation with an oncologist.

70. Bladder Cancer. Approve for 1 month if the patient meets ALL of the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has superficial papillary carcinoma of the urinary bladder; AND
- **C)** The medication is prescribed by or in consultation with an oncologist.

71. Breast Cancer. Approve for 6 months if the patient meets BOTH of the following (A and B):
- **A)** The patient is ≥ 18 years of age; AND
- **B)** The medication is prescribed by or in consultation with an oncologist.

72. Malignant Effusions. Approve for 6 months if the patient meets ALL of the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has intracavitary effusions secondary to diffuse or localized neoplastic disease; AND
- **C)** The medication is prescribed by or in consultation with an oncologist.

73. Ovarian Cancer. Approve for 6 months if the patient meets BOTH of the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

74. Hematopoietic Cell Transplanation. Approve for 1 month if the patient meets ALL of the following (A and B):
- **A)** Patient is undergoing one of the following (i, ii, or iii):
  - **i.** Autologous transplant; OR
  - **ii.** Allogeneic transplant; OR
  - **iii.** Umbilical cord blood transplant; AND
- **B)** The medication is prescribed by or in consultation with an oncologist.

75. Leptomeningeal Metastases. Approve for 6 months if the patient meets BOTH of the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The medication is prescribed by or in consultation with an oncologist.

76. Primary Central Nervous System Lymphoma. Approve for 3 months if the patient meets ALL of the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND

B) If thiotepa is given as conditioning for hematopoietic stem cell transplantation, it is given prior to transplantation; AND
C) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of thiotepa is not recommended in the following situations:

326. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1037. Tepadina® injection [prescribing information]. Lugano, Switzerland: Adienne; January 2017.
1038. Thiotepa for injection [prescribing information]. Schaumberg, IL: Sagent; April 2018.
1039. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 5.2023 – December 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed December 8, 2023.
1040. The NCCN Ovarian Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – June 2, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed December 8, 2023.
1041. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – May 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 8, 2023.
1042. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 1.2023 – March 24, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 8, 2023.
1043. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 8, 2023. Search term: thiotepa.
1044. The NCCN Hematopoietic Cell Transplantation (HCT) Clinical Practice Guidelines in Oncology (version 3.2023 – October 9, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 8, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Tivdak Prior Authorization Policy
- Tivdak™ (tisotumab vedotin-tftv intravenous infusion – Seagen and Genmab)

REVIEW DATE: 11/08/2023

OVERVIEW
Tivdak, a tissue factor-directed antibody and microtubule inhibitor conjugate, is indicated for the treatment of adults with recurrent or metastatic **cervical cancer** with disease progression on or after chemotherapy.[1]

Guidelines
The National Comprehensive Cancer Network (NCCN) cervical cancer (version 1.2024 – September 20, 2023) clinical practice guidelines recommend Tivdak for the second-line or subsequent therapy as a single agent for local/regional recurrence, stage IVB, or distant metastatic disease.[2,3]

Safety
Tivdak has a Boxed Warning for ocular toxicity.[1] Tivdak can cause changes in corneal epithelium and conjunctiva resulting in changes in vision, including severe vision loss, and corneal ulceration. Withhold, reduce the dose, or permanently discontinue Tivdak depending on the severity of ocular toxicity.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Tivdak. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tivdak as well as the monitoring required for adverse events and long-term efficacy, approval requires Tivdak to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Tivdak is recommended in those who meet the following criteria:

FDA-Approved Indication

77. Cervical Cancer. Approve for 1 year if the patient meets the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has tried at least one chemotherapy agent; AND
  Note: Examples of chemotherapy agents include cisplatin, carboplatin, paclitaxel, topotecan.
- **C)** Medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tivdak is not recommended in the following situations:

327. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1045. Tivdak™ intravenous infusion [prescribing information]. Bothell, WA: Seagen, and Plainsboro, NJ: Genmab; July 2023.

1046. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 6, 2023. Search term: tisotumab.

1047. The NCCN Cervical Cancer Clinical Practice Guidelines in Oncology (version 1.2024 – September 20, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 6, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Topotecan Products Prior Authorization Policy
- Hycamtin® (topotecan capsule – Novartis)
- Topotecan intravenous infusion (Hycamtin® – Novartis, generics)

REVIEW DATE: 01/18/2023

OVERVIEW

Topotecan injection, a topoisomerase inhibitor, is indicated for the treatment of patients with:
- **Cervical cancer**, stage IV-B, recurrent, or persistent disease which is not amenable to curative treatment, in combination with cisplatin.
- **Metastatic ovarian cancer**, after disease progression on or after initial or subsequent chemotherapy, as a single agent.
- **Small cell lung cancer** (SCLC), platinum-sensitive disease who progressed at least 60 days after initiation of first-line chemotherapy, as a single agent.[1]

Guidelines

Topotecan is included in a variety of National Comprehensive Cancer Network (NCCN) guidelines:
- **Bone cancer** (version 2.2023 – September 28, 2022) clinical practice guidelines recommend topotecan in combination with cyclophosphamide, as second-line therapy for patients with relapsed/refractory, or metastatic osteosarcoma and Ewing sarcoma (both category 2A), and dedifferentiated chondrosarcoma, high-grade undifferentiated pleomorphic sarcoma, and mesenchymal chondrosarcoma (category 2B).[2,7]
- **Central nervous system cancers** (version 2.2022 – September 29, 2022) clinical practice guidelines recommend topotecan as a single agent for the treatment of brain metastases in patients with small cell lung cancer.[2,8] In addition, the guidelines recommend intra-cerebrospinal fluid topotecan for the treatment of leptomeningeal metastases.
- **Cervical cancer** (version 1.2023 – January 6, 2023) clinical practice guidelines recommend topotecan as first-line, second-line, or subsequent therapy for patients with local/regional recurrence, stage IV-B disease, or distant metastases in combination with paclitaxel and bevacizumab (category 1), or in combination with paclitaxel or cisplatin (category 2A); or as a single agent in second-line and subsequent therapy.[2,5] It is also recommended as first-line, second-line and subsequent therapy for patients with persistent, recurrent, or metastatic small cell neuroendocrine carcinoma of the cervix (NECC) in combination with paclitaxel and bevacizumab. Topotecan can be used in combination with paclitaxel or cisplatin, or as a single agent (category 2A) for second-line or subsequent therapy of NECC.
- **Merkel cell carcinoma** (version 2.2022 – March 24, 2022) clinical practice guidelines recommend topotecan as a treatment option for patients with distant metastatic disease who have contraindications to checkpoint immunotherapy (Bavencio® [avelumab intravenous infusion], Keytruda® [pembrolizumab intravenous infusion], and Opdivo® [nivolumab intravenous infusion].[2,9]
- **Ovarian cancer** (version 1.2023 – December 22, 2022) clinical practice guidelines recommend topotecan, as a single agent or in combination with bevacizumab or sorafenib, for the treatment of recurrent or persistent platinum-resistant epithelial ovarian cancer, fallopian tube cancer, and peritoneal cancer.[2,3] Treatment of clinical relapse is a category 2A recommendation and immediate treatment of biochemical relapse is category 2B recommendation.

- **SCLC** (version 3.2023 – December 21, 2022) clinical practice guidelines recommend topotecan as a single agent for patients with a performance status of 0-2 and relapse following complete or partial response, or stable disease with initial treatment; or for primary progressive disease.[2,4]
- **Soft tissue sarcoma** (version 2.2022 – May 17, 2022) clinical practice guidelines recommend topotecan as a single agent or in combination with cyclophosphamide for the treatment of non-pleomorphic rhabdomyosarcoma.[2,10]
- **Uterine cancer** (version 1.2023 – December 22, 2022) clinical practice guidelines recommend topotecan as a single agent for the treatment of recurrent, metastatic, or high-risk endometrial carcinoma.[2,6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of topotecan. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with topotecan as well as the monitoring required for adverse events and long-term efficacy, approval requires topotecan to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of topotecan is recommended in those who meet one of the following criteria:

FDA-Approved Indications

78. Cervical Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets one of the following (i or ii):
  - **i.** Patient has persistent or recurrent disease; OR
  - **ii.** Patient has metastatic disease; AND
- **C)** Topotecan is prescribed by or in consultation with an oncologist.

79. Ovarian, Fallopian Tube, and Primary Peritoneal Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has persistent or recurrent disease; AND
- **C)** The cancer is platinum-resistant; AND
- **D)** Topotecan is prescribed by or in consultation with an oncologist.

80. Small Cell Lung Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets one of the following (i or ii):
  - **i.** Patient has relapsed disease; OR
  - **ii.** Patient has primary progressive disease; AND
- **C)** Topotecan will be used as a single agent; AND
- **D)** Topotecan is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

81. Bone Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
- **A)** Patient has one of the following (i, ii, iii, iv, or v):
  - **i.** Osteosarcoma; OR
  - **ii.** Ewing sarcoma; OR
  - **iii.** Dedifferentiated chondrosarcoma; OR
  - **iv.** High-grade undifferentiated pleomorphic sarcoma; OR
  - **v.** Mesenchymal chondrosarcoma; AND
- **B)** Patient has relapsed, refractory, or metastatic disease; AND
- **C)** Topotecan is used second-line; AND
- **D)** Topotecan is used in combination with cyclophosphamide; AND
- **E)** Topotecan is prescribed by or in consultation with an oncologist.

82. Brain Metastases. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has small cell lung cancer; AND
- **C)** Topotecan will be used as a single agent; AND
- **D)** Topotecan is prescribed by or in consultation with an oncologist.

83. Endometrial Carcinoma. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has recurrent, metastatic, or high-risk disease; AND
- **C)** Topotecan will be used as a single agent; AND
- **D)** Topotecan is prescribed by or in consultation with an oncologist.

84. Leptomeningeal and Spinal Metastases. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Topotecan will be administered intraventricularly; AND
- **C)** Topotecan is prescribed by or in consultation with an oncologist.

85. Merkel Cell Carcinoma. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has distant metastatic disease; AND
- **C)** Patient has contraindications to checkpoint immunotherapy; AND
  Note: Checkpoint immunotherapy includes Bavencio (avelumab intravenous infusion), Keytruda (pembrolizumab intravenous infusion), and Opdivo (nivolumab intravenous infusion).
- **D)** Topotecan is prescribed by or in consultation with an oncologist.

86. Rhabdomyosarcoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has non-pleomorphic rhabdomyosarcoma; AND
- **C)** Topotecan is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of topotecan is not recommended in the following situations:

328. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1048. Hycamtin® intravenous infusion [prescribing information]. East Hanover, NJ: Novartis; October 2019.
1049. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 11, 2023. Search term: topotecan.
1050. The NCCN Ovarian Cancer Clinical Practice Guidelines (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed January 12, 2023.
1051. The NCCN Small Cell Lung Cancer Clinical Practice Guidelines (version 3.2023 – December 21, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed January 12, 2023.
1052. The NCCN Cervical Cancer Clinical Practice Guidelines (version 1.2023 – January 6, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed January 12, 2023.
1053. The NCCN Uterine Cancer Clinical Practice Guidelines (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed January 12, 2023.
1054. The NCCN Bone Cancer Clinical Practice Guidelines (version 2.2023 – September 28, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed January 12, 2023.
1055. The NCCN Central Nervous System Cancers Clinical Practice Guidelines (version 2.2022 – September 29, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed January 12, 2023.
1056. The NCCN Merkel Cell Carcinoma Clinical Practice Guidelines (version 2.2022 – March 24, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed January 11, 2023.
1057. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines (version 2.2022 – May 17, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed January 12, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Torisel Prior Authorization Policy
- Torisel® (temsirolimus intravenous infusion – Wyeth)

REVIEW DATE: 12/13/2023

OVERVIEW
Torisel, an inhibitor of mammalian target of rapamycin (mTOR), is indicated for the treatment of **advanced renal cell carcinoma**.[1]

Guidelines
Torisel is addressed in National Comprehensive Cancer Network guidelines:
- **Kidney cancer:** Guidelines (version 1.2024 – June 21, 2023) recommend Torisel as a single agent for the treatment of relapsed or stage IV renal cell carcinoma.[2,3]
- **Soft tissue sarcoma:** Guidelines (version 2.2023 – April 25, 2023) recommend Torisel as a single agent for the treatment of perivascular epithelioid cell tumors (PEComas), lymphangioleiomyomatosis, and angiomyolipomas; and in combination with cyclophosphamide and vinorelbine for non-pleomorphic rhabdomyosarcoma.[2,4]
- **Uterine neoplasms:** Guidelines (version 1.2024 – September 20, 2023) recommend Torisel as a single-agent for the treatment of recurrent, metastatic, or high-risk endometrial cancer.[2,5]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Torisel. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Torisel as well as the monitoring required for adverse events and long-term efficacy, approval requires Torisel to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Torisel is recommended in those who meet one of the following criteria:

FDA-Approved Indication

87. Renal Cell Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has relapsed, advanced, or metastatic disease; AND
- **C)** Torisel will be used as a single-agent; AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

88. Endometrial Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has recurrent, metastatic, or high-risk disease; AND
- **C)** Patient has ONE of the following (i or ii):
  - **i.** Endometrial carcinoma; OR
  - **ii.** Uterine perivascular epithelioid cell tumor (PEComa); AND
- **D)** Torisel will be used as a single-agent; AND
- **E)** The medication is prescribed by or in consultation with an oncologist.

89. Soft Tissue Sarcoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has one of the following (i, ii, iii, or iv):
  - **i.** Perivascular epithelioid cell tumors (PEComas); OR
  - **ii.** Lymphangioleiomyomatosis; OR
  - **iii.** Recurrent angiomyolipoma; OR
  - **iv.** Non-pleomorphic rhabdomyosarcoma; AND
- **C)** Patient meets one of the following (i or ii):
  - **i.** Torisel will be used as a single-agent; OR
  - **ii.** Torisel will be used in combination with cyclophosphamide and vinorelbine; AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Torisel is not recommended in the following situations:

329. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1058. Torisel® intravenous infusion [prescribing information]. Philadelphia, PA: Wyeth; March 2018.
1059. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 8, 2023.
1060. The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (version 1.2024 – June 21, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 8, 2023.
1061. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 8, 2023.
1062. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (version 1.2024 – September 20, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 1, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Trastuzumab Products Prior Authorization Policy
- Herceptin® (trastuzumab intravenous infusion – Genentech)
- Herzuma® (trastuzumab-pkrb intravenous infusion – Celltrion)
- Kanjinti™ (trastuzumab-anns intravenous infusion – Amgen)
- Ogivri® (trastuzumab-dkst intravenous infusion – Mylan)
- Ontruzant® (trastuzumab-dttb intravenous infusion – Merck)
- Trazimera™ (trastuzumab-qyyp intravenous infusion – Pfizer)

REVIEW DATE: 06/28/2023

OVERVIEW

Trastuzumab products are human epidermal growth factor receptor 2 (HER2)/neu receptor antagonists indicated for the following uses:[1]

- **Breast cancer, adjuvant treatment** of HER2-overexpressing node positive or node negative (estrogen receptor [ER]/progesterone receptor [PR] negative or with one high risk feature) 1) as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel; 2) as part of treatment regimen with docetaxel and carboplatin; or 3) as a single agent following multi-modality anthracycline based therapy.
- **Breast cancer, metastatic,** HER2-overexpressing, either in combination with paclitaxel for first-line treatment, or as a single agent in patients who have received one or more chemotherapy regimens for metastatic disease.
- **Gastric cancer or gastroesophageal junction adenocarcinoma, metastatic**, HER2-overexpressing, in combination with cisplatin and capecitabine or 5-fluorouracil (5-FU) who have not received prior treatment for metastatic disease.

Herzuma, Kanjinti, Ogivri, Ontruzant, and Trazimera are all approved biosimilars for Herceptin; all of the biosimilars have the same FDA-approved indications as Herceptin. For all indications, patients must be selected for therapy based on an FDA-approved companion diagnostic for trastuzumab. Tests are specific for breast cancer or gastric cancer.

Guidelines

Trastuzumab is discussed in guidelines from the National Comprehensive Cancer Network (NCCN)

- **Breast Cancer:** NCCN guidelines (version 4.2023 – March 23, 2023) recommend trastuzumab in combination with chemotherapy or endocrine therapy for adjuvant treatment of HER2-positive breast cancer (category 1).[2,10] Trastuzumab in combination with paclitaxel (category 2A) is a preferred preoperative/adjuvant therapy regimen. The guidelines also list other trastuzumab-containing regimens for preoperative and adjuvant therapy. The preferred first-line agents for HER2-positive recurrent or metastatic disease (either hormone receptor-negative or hormone receptor-positive and refractory to endocrine therapy) include: Perjeta® (pertuzumab intravenous infusion) plus trastuzumab plus docetaxel (category 1) or paclitaxel (category 2A). The guidelines list other trastuzumab-containing regimens for HER2-positive metastatic disease.
- **Colon and Rectal Cancer:** NCCN guidelines for colon cancer (version 2.2023 – April 25, 2023) and NCCN guidelines for rectal cancer (version 3.2023 – May 26, 2023) list trastuzumab in combination with Perjeta, Tukysa (tucatinib tablets), or lapatinib tablets in patients with HER2-amplified disease, RAS and BRAF wild-type disease.[3-4,10]

- **Gastric Cancer and Esophageal and Esophagogastric Junction Cancers:** NCCN guidelines for Gastric Cancer (version 1.2023 – March 10, 2023) and Esophageal and Esophagogastric Junction Cancers (version 2.2023 – March 10, 2023) state that for metastatic, locally advanced or recurrent disease (where local therapy is not indicated) trastuzumab should be added to first-line systemic chemotherapy for HER2-overexpressing adenocarcinoma.[5,6,10] The recommended regimens for metastatic or locally advanced HER2-positive gastric, esophageal, or esophagogastric junction adenocarcinoma are trastuzumab in combination with cisplatin and a fluoropyrimidine (5-FU or capecitabine) [category 1] or trastuzumab in combination with other chemotherapy agents (category 2A/2B) [various regimens based on individual patient characteristics]. Trastuzumab is not recommended for use in combination with anthracyclines.
- **Head and Neck Cancers:** NCCN guidelines (version 2.2023- May 15, 2023) recommend trastuzumab as a systemic therapy option for recurrent, unresectable, or metastatic salivary gland tumors, (useful in certain circumstances), for HER2-positive tumors as a single agent or in combination with Perjeta or docetaxel (category 2A).[7,10]
- **Biliary Tract Cancers:** NCCN guidelines (version 2.2023 – May 10, 2023) recommend trastuzumab + Perjeta as subsequent-line therapy for biliary tract cancers for progression on or after systemic treatment for unresectable or metastatic disease that is HER2-positive (category 2A).[8,10]
- **Uterine Neoplasms**: NCCN guidelines (version 2.2023 – April 28, 2023) list the combination chemotherapy regimen of carboplatin/paclitaxel/trastuzumab as one of the recommended therapies for patients with HER2-positive endometrial carcinoma for stage III/IV or recurrent uterine serous carcinoma (category 2A).[9,10]

i.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of trastuzumab products. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with trastuzumab products, as well as the monitoring required for adverse events and long-term efficacy, approval requires trastuzumab products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of trastuzumab products is recommended in those who meet one of the following:

FDA-Approved Indications

74. Breast Cancer. Approve for the duration noted if the patient meets the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **C)** Patient meets ONE of the following criteria (i or ii):
  - **D) i.** Approve for 1 year (total) if trastuzumab is used for neoadjuvant (preoperative)/adjuvant therapy; OR
  - **E) ii.** Approve for 1 year if trastuzumab is used for recurrent or metastatic disease; AND
- **F)** The medication is prescribed by or in consultation with an oncologist.

75. Gastric, Esophageal, or Gastroesophageal Junction Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND

B) Patient has locally advanced or metastatic disease; AND
C) Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
D) Patient meets the following criteria (i and ii):
ii. Trastuzumab will be used as first-line therapy; AND
iii. Trastuzumab will be used in combination with chemotherapy; AND
Note: Examples of chemotherapy are cisplatin, oxaliplatin, capecitabine, 5-fluorouracil (5-FU).
E) The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

3. Biliary Tract Cancer. Approve for 1 year if the patient meets the following (A, B, C, D, E, and F):
A) Patient is ≥ 18 years of age; AND
B) Patient has unresectable or metastatic disease; AND
C) Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
D) The medication will be used in combination with Perjeta (pertuzumab intravenous infusion); AND
E) The patient has tried one systemic regimen; AND
G) Note: Examples of a systemic regimen include: gemcitabine and cisplatin, 5-fluorouracil and oxaliplatin, capecitabine and oxaliplatin, or gemcitabine and oxaliplatin.
F) The medication is prescribed by or in consultation with an oncologist.

4. Colon or Rectal Cancer. Approve for 1 year if the patient meets the following (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has advanced or metastatic disease; AND
C) Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
D) The medication is used in combination with Perjeta (pertuzumab intravenous infusion), lapatinib or Tukysa (tucatinib tablets); AND
E) The medication is prescribed by or in consultation with an oncologist.

5. Endometrial Carcinoma. Approve for 1 year if the patient meets the following (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has advanced or recurrent uterine serous carcinoma; AND
C) Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
D) Trastuzumab will be used in combination with chemotherapy; AND
H) Note: Examples of chemotherapy are carboplatin, paclitaxel.
E) The medication is prescribed by or in consultation with an oncologist.

6. Salivary Gland Tumor. Approve for 1 year if the patient meets the following (A, B, C, and D):
F) Patient is ≥ 18 years of age; AND
G) Patient has recurrent, unresectable, or metastatic disease; AND
H) Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
I) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of trastuzumab is not recommended in the following situations.

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

36. Herceptin® intravenous infusion [prescribing information]. South San Francisco, CA: Genentech; February 2021.
37. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – March 23, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 21, 2023.
38. The NCCN Colon Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 21, 2023.
39. The NCCN Rectal Clinical Practice Guidelines in Oncology (version 3.2023 – May 26, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 21 2023.
40. The NCCN Gastric Clinical Practice Guidelines in Oncology (version 1.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 21, 2023.
41. The NCCN Esophageal and Esophagogastric Junction Cancers Clinical Practice Guidelines in Oncology (version 2.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org Accessed on June 21, 2023.
42. The NCCN Head and Neck Cancers Clinical Practice Guidelines in Oncology (version 2.2023– May 15, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 21, 2023.
43. The NCCN Biliary Tract Cancers Clinical Practice Guidelines in Oncology (version 2.2023– May 15, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 21, 2023.
44. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (version 2.2023 – April 28, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 21, 2023.
45. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 21, 2023. Search term: trastuzumab.

G)

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Trodelvy Prior Authorization Policy
- Trodelvy® (sacituzumab govitecan-hziy intravenous infusion – Gilead)

REVIEW DATE: 12/20/2023

OVERVIEW

Trodelvy, a Trop-2-directed antibody and topoisomerase inhibitor conjugate, is indicated for the following uses in adults:[1]

- **Breast cancer**, unresectable locally advanced or metastatic triple-negative disease in adults who have received two or more prior systemic therapies, at least one of them for metastatic disease.
- **Breast cancer,** unresectable locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (immunohistochemistry [IHC] 0, IHC 1+ or IHC 2+/ISH–) breast cancer who have received endocrine based therapy and at least two additional systemic therapies in the metastatic setting.
- **Urothelial cancer**, locally advanced or metastatic disease in adults who have previously received a platinum-containing chemotherapy and either programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Guidelines

Trodelvy is addressed in National Comprehensive Cancer Network (NCCN) guidelines:

- **Bladder Cancer:** NCCN guidelines (version 3.2023 – May 25, 2023) list Trodelvy as an option for subsequent-line systemic therapy for locally advanced or metastatic disease (Stage IV) [Other Recommended Regimen; category 2A].[2] In cisplatin-eligible patients with locally advanced or metastatic disease, the first-line "Preferred Regimens" are gemcitabine and cisplatin or DDMVAC (dose-dense or accelerated course of methotrexate, vinblastine, doxorubicin, cisplatin) with growth factor support. Bavencio® (avelumab intravenous infusion) is the recommended maintenance regimen for either group.[2] For patients who are cisplatin ineligible, the "Preferred Regimens" are gemcitabine and carboplatin, followed by Bavencio for maintenance (category 1); and for patients whose tumors express PD-L1 or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression, the "Preferred Regimens" are Tecentriq® (atezolizumab intravenous infusion). Keytruda® (pembrolizumab intravenous infusion) is recommended for patients who are not eligible for any platinum-containing chemotherapy.
- **Breast Cancer:** NCCN guidelines (version 5.2023 – December 5, 2023) list Trodelvy as a "Preferred Regimen" for patients with metastatic triple-negative breast cancer who have received at least two prior therapies, with at least one for metastatic disease (category 1); it may be considered for later line if not used a second line therapy.[3] Trodelvy is also a "Preferred Regimen" for patients with HR positive, HER2 negative cancers after prior treatment, including endocrine therapy, a cyclin dependent kinase (CDK) 4/6 inhibitor, and at least two lines of chemotherapy (one of which was a taxane, and at least one of which was in the metastatic setting) for advanced breast cancer (category 1). It may be considered for later line if not used a second-line therapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Trodelvy. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Trodelvy as well as the monitoring required for adverse events and long-term efficacy, approval requires Trodelvy to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Trodelvy is recommended in those who meet one of the following criteria:

FDA-Approved Indications

76. Breast Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has human epidermal growth factor receptor 2 (HER2)- negative breast cancer; AND
- **C)** Patient has recurrent or metastatic disease; AND
- **D)** Patient meets ONE of the following (i or ii):
  - **i.** Patient meets BOTH of the following (a and b):
    - **a)** Patient has hormone receptor (HR) negative disease; AND
    - **b)** Patient has tried at least two systemic regimens; OR

      A) Note: Examples of systemic regimens include: cisplatin, carboplatin, doxorubicin, liposomal doxorubicin, paclitaxel, capecitabine, gemcitabine, vinorelbine, Halaven (eribulin intravenous infusion), Keytruda (pembrolizumab intravenous infusion) + chemotherapy (Abraxane [albumin-bound paclitaxel intravenous infusion], paclitaxel, or gemcitabine and carboplatin).
  - **ii.** Patient meets ALL of the following (a, b, c, and d):
    - **a)** Patient has hormone receptor (HR) positive disease; AND
    - **b)** Patient has tried endocrine therapy; AND
    - **c)** Patient has tried a cyclin-dependent kinase (CDK) 4/6 inhibitor; AND

      B) Note: Examples of CDK4/6 inhibitors include: Kisqali (ribociclib tablets), Ibrance (palbociclib capsules or tablets), or Verzenio (abemaciclib tablets).
    - **d)** Patient has tried at least two systemic chemotherapy regimens; AND

      C) Note: Examples of chemotherapy regimens include: paclitaxel, cisplatin, carboplatin, doxorubicin, liposomal doxorubicin, gemcitabine, vinorelbine, Halaven (eribulin intravenous infusion).
- **E)** The medication is prescribed by or in consultation with an oncologist.

2. Urothelial Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
- **D)** Patient is ≥ 18 years of age; AND
- **E)** Patient has locally advanced or metastatic urothelial cancer; AND
- **F)** Patient has tried at least one systemic chemotherapy; AND

  G) Note: Examples of systemic chemotherapy include cisplatin, carboplatin, gemcitabine, paclitaxel, ifosfamide, doxorubin.
- **H)** Patient has tried at least one programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor; AND

  I) Note: Examples of PD-1 and PD-L1 inhibitors include Bavencio (avelumab intravenous infusion), Keytruda (pembrolizumab intravenous infusion), Opdivo (nivolumab intravenous infusion), Tecentriq (atezolizumab intravenous infusion).

J) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Trodelvy is not recommended in the following situations:

10. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

46. Trodelvy® intravenous injection [prescribing information]. Morris Plains, NJ: Gilead; February 2023.
47. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – May 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 18, 2023.
48. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 5.2023 – December 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 18, 2023.

11.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Unituxin Prior Authorization Policy
- Unituxin® (dinutuximab intravenous infusion – United Therapeutics)

REVIEW DATE: 12/20/2023

OVERVIEW
Unituxin, a glycolipid disialoganglioside (GD2)-binding monoclonal antibody, is indicated for the treatment of pediatric patients with high-risk **neuroblastoma** who achieve at least a partial response to prior first-line multi-agent, multimodality therapy, in combination with granulocyte-macrophage colony-stimulating factor, interleukin-2, and 13-cis-retinoic acid.[1]

Guidelines
Unituxin is not addressed in National Comprehensive Cancer Network treatment guidelines.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Unituxin. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Unituxin as well as the monitoring required for adverse events and long-term efficacy, approval requires Unituxin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Unituxin is recommended in those who meet the following criteria:

FDA-Approved Indication

90. Neuroblastoma. Approve for 6 months if the patient meets the following (A, B, and C):
- **A)** Patient is ≤ 18 years of age; AND
- **B)** Unituxin is used as subsequent therapy; AND
- **C)** Unituxin is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Unituxin is not recommended in the following situations:

330. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1063. Unituxin intravenous infusion [prescribing information]. Silver Spring, ND: United Therapeutics; September 2020.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Vectibix Prior Authorization Policy
- Vectibix® (panitumumab intravenous infusion – Amgen)

REVIEW DATE: 08/02/2023

OVERVIEW

Vectibix, an epidermal growth factor receptor monoclonal antibody, is indicated for the treatment of wild-type *RAS* (defined as wild-type in both KRAS and NRAS as determined by an FDA-approved test for this use) **metastatic colorectal cancer** (mCRC) as:[1]

- First-line therapy in combination with FOLFOX (5-fluorouracil [5-FU], leucovorin, oxaliplatin).
- Monotherapy following disease progression after prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy.

Limitation of Use: Vectibix is not indicated for the treatment of patients with *RAS*-mutant mCRC or for whom *RAS* mutation status is unknown.

Guidelines

The National Comprehensive Cancer Network (NCCN) **Colon Cancer** guidelines (version 2.2023 – April 25, 2023) recommend Vectibix as primary therapy for unresectable, advanced, or metastatic *KRAS/NRAS/BRAF* wild-type gene and left-sided tumors only in combination with irinotecan, FOLFOX, FOLFIRI (5-FU, leucovorin, irinotecan), or FOLFOXIRI (5-FU, leucovorin, oxaliplatin, irinotecan) regimens in patients who can tolerate intensive therapy or as a single agent in patients who cannot tolerate intensive therapy.[2,4] Reference to left-sided only disease refers to a primary tumor that originated in the left side of the colon. Therapies recommended after first progression vary depending on the initial treatment regimen (i.e., 5-FU/leucovorin-based or capecitabine-based therapy) that was used. The NCCN guidelines recommend Vectibix, in combination with irinotecan, FOLFOX, or FOLFIRI for the subsequent treatment of *KRAS/NRAS/BRAF* wild-type tumors; or in combination with Braftovi® (encorafenib capsules) for the subsequent treatment of *BRAF V600E* positive disease. The NCCN **Rectal Cancer** guidelines (version 3.2023 – May 26, 2023) make the same recommendations for Vectibix for the treatment of rectal cancer.[3,4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vectibix. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vectibix as well as the monitoring required for adverse events and long-term efficacy, approval requires Vectibix to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vectibix is recommended in those who meet the following criteria:

FDA-Approved Indication

47. Colon and Rectal Cancer. Approve for 1 year if the patient meets the following (A, B, C, D, E, and F):

A) Patient is ≥ 18 years of age; AND

B) Patient has unresectable, advanced, or metastatic disease; AND

C) Patient's tumor or metastases are wild-type *RAS* (*KRAS* wild-type and *NRAS* wild-type) [that is, the tumor or metastases are *KRAS* and *NRAS* mutation negative]; AND

D) The primary tumor originated on the left side of the colon (from splenic flexure to rectum); AND

E) Patient meets ONE of the following (i or ii):

i. Patient's tumor or metastases are wild-type *BRAF* (that is, the tumor or metastases are *BRAF V600E* mutation negative); OR

ii. Patient's tumor or metastases are *BRAF V600E* mutation-positive and the patient meets BOTH of the following (a and b):

a) Patient has previously received a chemotherapy regimen for colon or rectal cancer; AND

Note: Examples of chemotherapy regimens include a fluoropyrimidine such as 5-fluorouracil (5-FU), capecitabine, oxaliplatin, irinotecan, or an adjunctive chemotherapy regimen such as FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).

b) Vectibix is prescribed in combination with Braftovi (encorafenib capsules); AND

F) Vectibix is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vectibix is not recommended in the following situations:

331. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

58. Vectibix® intravenous infusion [prescribing information]. Thousand Oaks, CA: Amgen; August 2021.
59. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 25, 2023.
60. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – May 26, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 25, 2023.
4. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 25, 2023. Search term: panitumumab.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Vyxeos Prior Authorization Policy
- Vyxeos® (daunorubicin and cytarabine liposome intravenous infusion – Jazz)

REVIEW DATE: 12/13/2023

OVERVIEW

Vyxeos is a liposomal combination of daunorubicin, an anthracycline topoisomerase inhibitor, and cytarabine, a nucleoside metabolic inhibitor, is indicated for the treatment of newly-diagnosed therapy-related **acute myeloid leukemia** (AML) or **AML with myelodysplasia-related changes** in patients ≥ 1 year of age.[1]

Guidelines

The National Comprehensive Cancer Network guidelines for **acute myeloid leukemia** (version 6.2023 – October 24, 2023) recommend Vyxeos for induction and post-remission therapy for patients with therapy-related AML, antecedent myelodysplastic syndrome/chronic myelomonocytic leukemia, and AML with myelodysplasia-related changes.[2,3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vyxeos. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vyxeos as well as the monitoring required for adverse events and long-term efficacy, approval requires Vyxeos to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vyxeos is recommended in those who meet the following criteria:

FDA-Approved Indication

91. Acute Myeloid Leukemia. Approve for 6 months if the patient meets the following (A, B, and C):
- **A)** Patient is ≥ 1 year of age; AND
- **B)** Patient meets one of the following (i or ii):
  - **i.** Patient has therapy-related acute myeloid leukemia; OR
  - **ii.** Patient has secondary acute myeloid leukemia; AND
    Note: Examples include antecedent myelodysplastic syndrome/chronic myelomonocytic leukemia and acute myeloid leukemia with myelodysplasia-related changes.
- **C)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vyxeos is not recommended in the following situations:

332. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1064. Vyxeos liposome intravenous infusion [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals; September 2022.
1065. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 8, 2023. Search term: Vyxeos.
1066. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 6.2023 – October 24, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 8, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Yervoy Prior Authorization Policy
- Yervoy® (ipilimumab intravenous infusion – Bristol-Myers Squibb)

REVIEW DATE: 12/06/2023

OVERVIEW

Yervoy, a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody, is indicated for the following uses:[1]

- **Colorectal cancer, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)**, in combination with Opdivo® (nivolumab intravenous infusion) for the treatment of patients ≥ 12 years of age with metastatic disease that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- **Esophageal cancer**, in combination with Opdivo for the first-line treatment of adults with unresectable advanced or metastatic esophageal squamous cell carcinoma.
- **Hepatocellular carcinoma**, in combination with Opdivo, for the treatment of adults who have been previously treated with Nexavar® (sorafenib tablets). This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- **Malignant pleural mesothelioma**, in combination with Opdivo, for the first-line treatment of adults with unresectable disease.
- **Melanoma**, unresectable or metastatic disease in patients ≥ 12 years of age, as a single agent or in combination with Opdivo.
- **Melanoma**, for adjuvant treatment of cutaneous disease in patients with pathologic involvement of regional lymph nodes of > 1 mm who have undergone complete resection, including total lymphadenectomy.
- **Non-small cell lung cancer (NSCLC)**, in combination with Opdivo, for the first-line treatment of adults with metastatic disease whose tumors express programmed death ligand-1 (PD-L1) [≥ 1%], as determined by an FDA-approved test, with no epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations.
- **NSCLC**, in combination with Opdivo and two cycles of platinum-doublet chemotherapy, for the first-line treatment of adults with metastatic or recurrent NSCLC, with no *EGFR* or *ALK* genomic tumor aberrations.
- **Renal cell carcinoma (RCC)**, advanced, in combination with Opdivo for the treatment of patients with intermediate or poor risk, previously untreated disease.

A)

Guidelines

The National Comprehensive Cancer Network Compendium recommends Yervoy for the following conditions: melanoma (uveal, cutaneous, and brain metastases), bone cancer, small bowel adenocarcinoma, ampullary adenocarcinoma, kidney cancer, malignant pleural mesothelioma, colon and rectal cancer, gastric cancer, esophageal and esophagogastric junction cancer, hepatocellular carcinoma, biliary tract cancer, Kaposi sarcoma, Merkel cell carcinoma, soft tissue sarcoma, neuroendocrine tumors, and NSCLC.[2]

POLICY STATEMENT

iii. Prior Authorization is recommended for prescription benefit coverage of Yervoy. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Yervoy as well as the monitoring required for adverse events and long-term efficacy, approval requires the medication to be prescribed by or in consultation with a prescriber who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Yervoy is recommended in those who meet one of the following criteria:

FDA-Approved Indications

20. Colon, Rectal, or Appendiceal Cancer. Approve for 4 months if the patient meets ALL of the following (A, B, C, and D):
- **A)** Patient is ≥ 12 years of age; AND
- **B)** The tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND
- **C)** The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

21. Esophageal and Esophagogastric Junction Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following (i or ii):
  - **i.** Patient meets ALL of the following (a, b, c, and d):
    - **a)** Patient has squamous cell carcinoma; AND
    - **b)** Patient has unresectable, advanced, or metastatic disease; AND
    - **c)** According to the prescriber, the patient is not a surgical candidate; AND
    - **d)** The medication will be used for first-line therapy; OR
  - **ii.** The tumor is microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR); AND
- **C)** The medication will be used in combination with Opdivo (nivolumab intravenous infusion); AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

22. Hepatocellular Carcinoma. Approve for 4 months if the patient meets ALL of the following (A, B, C, D, E, and F):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has Child-Pugh Class A liver function; AND
- **C)** According to the prescriber, the patient has ONE of the following (i, ii, or iii):
  - **iv.** Unresectable disease and is not a transplant candidate; OR
  - **v.** Liver-confined disease, inoperable by performance status, comorbidity, or with minimal or uncertain extrahepatic disease; OR
  - **vi.** Metastatic disease or extensive liver tumor burden; AND
- **D)** The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
- **E)** Patient has tried at least one tyrosine kinase inhibitor; AND
  - **B)** Note: Examples are Nexavar (sorafenib tablets), Lenvima (levatinib capsules).
- **F)** The medication is prescribed by or in consultation with an oncologist.

23. Melanoma. Approve for the duration noted if the patient meets ALL of the following (A, B, and C):
Note: This includes cutaneous melanoma, brain metastases due to melanoma, and uveal melanoma.

A) Patient is ≥ 12 years of age; AND

B) Patient meets ONE of the following (i or ii):

a) Approve for 4 months if the patient has unresectable, recurrent, or metastatic melanoma; OR

b) Approve for 1 year if Yervoy is used as adjuvant treatment; AND

C) Note: For example, in patients with cutaneous melanoma who have undergone complete resection, including total lymphadenectomy.

C) The medication is prescribed by or in consultation with an oncologist.

24. Mesothelioma. Approve for 1 year if the patient meets the following (A, B, C, and D):

a) Patient is ≥ 18 years of age; AND

b) Patient has ONE of the following (i, ii, iii, or iv):

a. Malignant pleural mesothelioma; OR
b. Malignant peritoneal mesothelioma; OR
c. Pericardial mesothelioma; OR
d. Tunica vaginalis testis mesothelioma; AND

c) The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND

d) The medication is prescribed by or in consultation with an oncologist.

D)

25. Non-Small Cell Lung Cancer (NSCLC). Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

a) Patient is ≥ 18 years of age; AND

b) Patient has recurrent, advanced, or metastatic disease; AND

c) Patient meets one of the following (i, ii, or iii):

a. Yervoy is used as first-line or continuation maintenance therapy and the patient meets BOTH of the following (a and b):

E) Note: This is regardless of PD-L1 status.

i. The medication will be used in combination with Opdivo (nivolumab intravenous infusion); AND

ii. The tumor is negative for actionable mutations; OR

F) Note: Examples of actionable mutations include sensitizing epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *NRTK* gene fusion-positive, *ROS1, BRAF V600E, MET 14* skipping mutation, *RET* rearrangement.

b. Yervoy is used as first-line therapy and the patient meets BOTH of the following (a and b):

a) The tumor is positive for one of the following mutations [(1), (2), or (3)]:

(1) Epidermal growth factor receptor (*EGFR*) exon 20 mutation; OR

(2) *KRAS G12C* mutation; OR

(3) *ERBB2* (HER2) mutation; AND

b) The medication will be used in combination with Opdivo (nivolumab intravenous infusion); OR

iv. Yervoy is used as first-line or subsequent therapy and the patient meets BOTH of the following (a and b):

a) The tumor is positive for one of the following mutations [(1), (2), (3), or (4)]:

(1) *BRAF V600E* mutation; OR

(2) *NTRK1/2/3* gene fusion; OR

(3) *MET* exon 14 skipping mutation; OR

(4) *RET* rearrangement; AND

b) The medication will be used in combination with Opdivo (nivolumab intravenous infusion); OR

v. Yervoy is used as subsequent therapy and the patient meets ALL of the following (a, b, and c):

a) Tumor is positive for one of the following [(1), (2), (3), or (4)]:

(1) Epidermal growth factor receptor (*EGFR*) exon 19 deletion or exon 21 *L858R* mutation; OR

(2) Epidermal growth factor receptor (*EGFR*) *S768I, L861Q*, and/or *G719X* mutation; OR

(3) *ALK* rearrangement; OR

(4) *ROS1* rearrangement; AND

b) The patient has received targeted drug therapy for the specific mutation; AND

G) Note: Examples of targeted drug therapy include Gilotrif (afatinib tablets), Tagrisso (osimertinib tablets), erlotinib, Iressa (gefitinib tablets), Xalkori (crizotinib capsules), Zykadia (ceritinib capsules), Alecensa (alectinib capsules), Alunbrig (brigatinib tablets), Lorbrena (lorlatinib tablets), Rozlytrek (entrectinib capsules), or Vizimpro (dacomitinib tablets).

c) Yervoy is used in combination with Opdivo (nivolumab intravenous infusion); AND

D) The medication is prescribed by or in consultation with an oncologist.

26. Renal Cell Carcinoma. Approve for 4 months if the patient meets the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient has advanced, relapsed, or metastatic disease; AND

C) The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND

D) The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

27. Ampullary Adenocarcinoma. Approve for 4 months if the patient meets the following (A, B, C, D, E, and F):

A) Patient is ≥ 18 years of age; AND

B) Patient has intestinal type disease; AND

C) Patient has progressive, unresectable, or metastatic disease; AND

D) The tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND

E) The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND

F) The medication is prescribed by or in consultation with an oncologist.

28. Biliary Tract Cancer. Approve for 1 year if the patient meets the following (A, B, C, D, E, F, and G):

A) Patient is ≥ 18 years of age; AND

B) Patient has unresectable, resected with gross residual, or metastatic disease; AND

C) Medication is used as subsequent therapy; AND

D) Patient has tumor mutation burden-high (TMB-H) disease; AND

H) Note: TMB-H is defined as 10 or more mutations per megabase.

E) Patient has ONE of the following (i, ii, or iii):

i. Gallbladder cancer; OR

ii. Intrahepatic cholangiocarcinoma; OR

iii. Extrahepatic cholangiocarcinoma; AND

F) The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND

G) The medication is prescribed by or in consultation with an oncologist.

29. Bone Cancer. Approve for 1 year if the patient meets the following (A, B, C, D, E, F, and G):

A) Patient is ≥ 12 years of age; AND

B) Patient has unresectable or metastatic disease; AND
C) Patient has progressed following prior treatment; AND
D) Patient has tumor mutation burden-high (TMB-H) disease; AND
I) Note: TMB-H is defined as 10 or more mutations per megabase.
E) Patient has one of the following (i, ii, iii, iv, or v):
i. Chondrosarcoma; OR
J) Note: Includes mesenchymal chondrosarcoma and dedifferentiated chondrosarcoma.
ii. Chordoma; OR
iii. Ewing sarcoma; OR
iv. High-grade undifferentiated pleomorphic sarcoma; OR
v. Osteosarcoma; AND
F) The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
G) The medication is prescribed by or in consultation with an oncologist.

30. Gastric Cancer. Approve for 4 months if the patient meets the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) The tumor is microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR); AND
C) The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
D) The medication is prescribed by or in consultation with an oncologist.

31. Kaposi Sarcoma. Approve for 1 year if the patient meets the following (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has classic Kaposi sarcoma; AND
C) Patient has relapsed or refractory disease; AND
D) The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
E) The medication is prescribed by or in consultation with an oncologist.

32. Merkel Cell Carcinoma. Approve for 4 months if the patient meets the following (A and B):
A) Patient is ≥ 18 years of age; AND
B) The medication is prescribed by or in consultation with an oncologist.

14. Neuroendocrine Tumors. Approve for 1 year if the patient meets the following (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has advanced or metastatic disease; AND
C) Patient meets one of the following (i, ii, iii, or iv):
i. Patient has well differentiated, Grade 3 disease; OR
ii. Patient has extrapulmonary poorly differentiated neuroendocrine carcinoma; OR
iii. Patient has large or small cell disease carcinoma; OR
iv. Patient has mixed neuroendocrine-non-neuroendocrine neoplasm; AND
D) The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
E) The medication is prescribed by or in consultation with an oncologist.

15. Small Bowel Adenocarcinoma. Approve for 1 year if the patient meets the following (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has advanced or metastatic disease; AND
C) The tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND
D) The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
E) The medication is prescribed by or in consultation with an oncologist.

16. Soft Tissue Sarcoma. Approve for 1 year if the patient meets the following (A, B, C, D, and E):

A) Patient is ≥ 18 years of age; AND
B) Patient has advanced, unresectable, or metastatic disease; AND
C) Patient has ONE of the following (i, ii, iii, or iv)
  i. Extremity/body wall, head/neck disease; OR
  ii. Retroperitoneal/intra-abdominal disease; OR
  iii. Rhabdomyosarcoma; OR
  iv. Angiosarcoma; AND
D) The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
E) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Yervoy is not recommended in the following situations:

148. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

288. Yervoy® intravenous infusion [prescribing information]. Bridgewater, NJ: Sanofi-Aventis; February 2023.
289. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 28, 2023. Search term: ipilimumab.
290. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – November 16, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 4, 2023.
291. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 6.2023 – November 16, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 4, 2023.
292. The NCCN Hepatocellular Carcinoma Clinical Practice Guidelines in Oncology (version 2.2023 – September 14, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 30, 2023.
293. The NCCN Melanoma: Cutaneous Clinical Practice Guidelines in Oncology (version 3.2023 – October 27, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 30, 2023.
294. The NCCN Uveal Melanoma Clinical Practice Guidelines in Oncology (version 1.2023 – May 4, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 30, 2023.
295. The NCCN Mesothelioma: Pleural Clinical Practice Guidelines in Oncology (version 1.2024 – November 21, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 4, 2023.
296. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 5.2023 – November 8, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 4, 2023.
297. The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (version 1.2024 – June 21, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 30, 2023.
298. The NCCN Neuroendocrine and Adrenal Tumors Clinical Practice Guidelines in Oncology (version 1.2023 – August 2, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 30, 2023.
299. The NCCN Small Bowel Adenocarcinoma Clinical Practice Guidelines in Oncology (version 1.2023 – January 9, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 30, 2023.
300. The NCCN Esophageal and Esophagogastric Junction Cancers Clinical Practice Guidelines in Oncology (version 3.2023 – August 29, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed December 4, 2023.
301. The NCCN Bone Cancer Clinical Practice Guidelines in Oncology (version 1.2024 – August 7, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 30, 2023.
302. The NCCN Ampullary Adenocarcinoma Clinical Practice Guidelines in Oncology (version 2.2023 – August 3, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 30, 2023.
303. The NCCN Mesothelioma: Peritoneal Clinical Practice Guidelines in Oncology (version 1.2024 – November 21, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 4, 2023.
304. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 1.2023 – March 24, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 30, 2023.

305. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 30, 2023.
306. The NCCN Kaposi Sarcoma Clinical Practice Guidelines in Oncology (version 1.2024 – November 7, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 30, 2023.
307. The NCCN Gastric Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – August 29, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 30, 2023.
308. The NCCN Biliary Tract Cancers Clinical Practice Guidelines in Oncology (version 3.2023 – November 8, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 4, 2023.
309. The NCCN Merkel Cell Carcinoma Clinical Practice Guidelines in Oncology (version 1.2024 – November 22, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 4, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Zaltrap Prior Authorization Policy
- Zaltrap® (ziv-aflibercept intravenous infusion – Regeneron/Sanofi-Aventis)

REVIEW DATE: 10/11/2023

OVERVIEW

Zaltrap, a recombinant fusion protein, in combination with FOLFIRI (5-fluorouracil [5-FU], leucovorin, and irinotecan), is indicated for patients with **metastatic colorectal cancer** that is resistant to or has progressed following an oxaliplatin-containing regimen.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) **colon cancer** guidelines (version 3.2023 – September 21, 2023) and **rectal cancer** guidelines (version 5.2023 – September 21, 2023) recommend Zaltrap as: [2-4]

- Initial treatment for patients with unresectable metachronous metastases and previous FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) regimens within the past 12 months in combination with irinotecan OR with FOLFIRI, or
- Subsequent therapy after first progression of unresectable advanced or metastatic disease in combination with irinotecan or with FOLFIRI for disease not previously treated with an irinotecan-based regimen.

Both of these uses have a category 2A recommendation. Zaltrap has a category 2B recommendation for use as adjuvant therapy, in combination with FOLFIRI or irinotecan, for unresectable metachronous metastases that convert to resectable disease after primary treatment.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zaltrap. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zaltrap as well as the monitoring required for adverse events and long-term efficacy, approval requires Zaltrap to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zaltrap is recommended in those who meet the following criteria:

FDA-Approved Indication

92. Colon and Rectal Cancer, Appendiceal Adenocarcinoma. Approve for 1 year if the patient meets the following (A, B, C, D, E, and F):
- **56.** Patient is ≥ 18 years of age; AND
- **57.** Patient has advanced or metastatic disease; AND
- **58.** Patient has been previously treated with an oxaliplatin- or fluoropyrimidine-containing regimen; AND

Note: Fluoropyrimidines include 5-fluorouracil (5-FU) and capecitabine.

59. Patient has not previously been treated with FOLFIRI; AND

Note: FOLFIRI includes 5-fluorouracil (5-FU), leucovorin, and irinotecan.

60. Zaltrap will be used in combination with 5-fluorouracil (5-FU) or capecitabine, and/or irinotecan; AND

61. The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zaltrap is not recommended in the following situations:

333. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1067. Zaltrap® intravenous infusion [prescribing information]. Bridgewater, NJ: Regeneron/Sanofi-Aventis; June 2020.

1068. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – September 21, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 5, 2023.

1069. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 5.2023 – September 21, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 5, 2023.

1070. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 5, 2023. Search term: ziv-aflibercept.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Zepzelca Prior Authorization Policy
- Zepzelca™ (lurbinectedin intravenous infusion – Jazz)

REVIEW DATE: 06/28/2023

OVERVIEW

Zepzelca, an alkylating drug, is indicated for the treatment of metastatic **small cell lung cancer** in adults with disease progression on or after platinum-based chemotherapy.[1] This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Guidelines

The National Comprehensive Cancer Network (NCCN) Small Cell Lung Cancer guidelines (version 3.2023 – December 21, 2022) recommend Zepzelca as a single agent for the treatment of relapsed disease following a complete or partial response, or stable disease with initial treatment, or for the treatment of primary progressive disease.[2,3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zepzelca. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zepzelca as well as the monitoring required for adverse events and long-term efficacy, approval requires Zepzelca to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zepzelca is recommended in those who meet the following:

FDA-Approved Indication

93. Small Cell Lung Cancer. Approve for 1 year if the patient meets the following (A, B, and C):
- **A)** Patient has metastatic disease; AND
- **B)** Patient has previously received platinum-based chemotherapy; AND
  Note: Examples of platinum medications include cisplatin and carboplatin.
- **C)** Zepzelca is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zepzelca is not recommended in the following situations:

334. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1071. Zepzelca intravenous infusion [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals; April 2022.
1072. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 23, 2023. Search term: lurbinectedin.
1073. The NCCN Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – December 21, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 23, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Zynlonta Prior Authorization Policy
- Zynlonta® (loncastuximab tesirine-lpyl intravenous infusion – Teva)

REVIEW DATE: 05/31/2023

OVERVIEW

Zynlonta, a CD19-directed antibody and alkylating agent conjugate, is indicated for the treatment of relapsed or refractory **large B-cell lymphoma** (including diffuse large B-cell lymphoma [DLBCL] not otherwise specified, DLBCL arising from low grade lymphoma, and high grade B-cell lymphoma) in adults, after two or more lines of systemic therapy.[1] Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Guidelines

Zynlonta is discussed in the guidelines from the National Comprehensive Cancer Network (NCCN):

- **B-Cell Lymphoma**: NCCN guidelines (version 3.2023 – May 11, 2023) recommend Zynlonta as a third-line and subsequent therapy option only after two or more lines of systemic therapy.[2] For second-line or subsequent treatment of relapsed or refractory DLBCL, a variety of chemotherapy-based regimens ± rituximab are preferred regimens. Allogeneic stem cell transplantation is also an option for selected patients, as consolidation after alternate second-line therapy. NCCN notes that it is unclear if any CD-19 therapy (including Zynlonta and Monjuvi® [tafasitamab intravenous infusion]) would have a negative impact on the clinical efficacy of subsequent anti-CD19 CAR T-cell therapy.[2,3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zynlonta. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zynlonta as well as the monitoring required for adverse events and long-term efficacy, approval requires Zynlonta to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zynlonta is recommended in those who meet the following criteria:

FDA-Approved Indication

94. Large B-Cell Lymphoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
Note: This includes diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma.
A) Patient is ≥ 18 years of age; AND
B) Patient has tried at least two systemic regimens; AND

Note: Examples of systemic therapies containing one or more of the following products include gemcitabine, oxaliplatin, rituximab, Polivy (polatuzumab vedotin intravenous infusion), bendamustine, Monjuvi (tafasitamab-cxix intravenous infusion), or Revlimid (lenalidomide capsules). Autologous stem cell transplant and chimeric antigen receptor (CAR) T-cell therapy also count as a systemic regimen.

C) The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

95. Human Immunodeficiency Virus-Related B-Cell Lymphoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):

Note: This includes human immunodeficiency virus-related diffuse large B-cell lymphoma (DLBCL), primary effusion lymphoma, and human herpes virus 8 (HHV8)-positive DLBCL not otherwise specified.

A) Patient is ≥ 18 years of age; AND

B) Patient has tried at least two systemic regimens; AND

Note: Examples of systemic therapies include R-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab) and RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone).

C) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zynlonta is not recommended in the following situations:

335. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1074. Zynlonta® intravenous infusion [prescribing information]. Murray Hill, NJ: ADC Therapeutics; October 2022.

1075. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 3.2023 – May 11, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 15, 2023.

1076. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Search term: loncastuximab. Accessed on May 15, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Other) – Adstiladrin Prior Authorization Policy
- Adstiladrin® (nadofaragene firadenovec-vncg intravesical suspension – Ferring)

REVIEW DATE: 06/14/2023

OVERVIEW
Adstiladrin, a non-replicating adenoviral vector-based gene therapy, is indicated for the treatment of high-risk Bacillus Calmette-Guerin (BCG)-unresponsive non-muscle invasive **bladder cancer** (NMIBC) with carcinoma *in situ* (CIS) with or without papillary tumors in adults.[1]

Guidelines
The National Comprehensive Cancer Network (NCCN) **bladder cancer** clinical guidelines (version 2.2023 – April 25, 2023) recommend Adstiladrin for the treatment of BCG-unresponsive, high-risk NMIBC with CIS with or without papillary tumors (category 2A) and BCG-unresponsive, high-risk NMIBC with high-grade papillary Ta/T1 tumors without CIS (category 2B) as initial treatment or for cytology- and bladder-biopsy positive, imaging- and cystoscopy-negative, recurrent or persistent disease.[2,3]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Adstiladrin. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Adstiladrin as well as the monitoring required for adverse events and long-term efficacy, approval requires Adstiladrin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Adstiladrin is recommended in those who meet the following criteria:

FDA-Approved Indication

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96. Non-Muscle Invasive Bladder Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has high-risk, Bacillus Calmette-Guerin (BCG)-unresponsive disease; AND
- **C)** Patient meets ONE of the following (i or ii):
  - **i.** Patient has carcinoma *in situ* (CIS) with or without high-grade papillary Ta/T1 tumors; OR
  - **ii.** Patient has high-grade papillary Ta/T1 tumors without CIS; AND
- **D)** Medication is used for ONE of the following (i or ii):
  - **i.** Initial treatment; OR
  - **ii.** Cytology- and bladder-biopsy positive, imaging- and cystoscopy-negative, recurrent or persistent disease; AND
- **E)** Medication is prescribed by or in consultation with an urologist or an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Adstiladrin is not recommended in the following situations:

336. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1077. Adstiladrin intravesical suspension [prescribing information]. Kastrup, Denmark: Ferring; December 2022.
1078. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (Version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 9, 2023.
1079. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Search term: nadofaragene. Accessed on June 9, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Other) – Jelmyto Prior Authorization Policy
- Jelmyto® (mitomycin solution for pyelocalyceal administration – UroGen)

REVIEW DATE: 05/10/2023

OVERVIEW
Jelmyto, an alkylating agent, is indicated for the treatment of low-grade upper tract **urothelial cancer** in adults.[1]

Dosing Information
Jelmyto is for pyelocalyceal use only.[1] The recommended dose is 4 mg/mL of mitomycin administered by ureteral catheter or a nephrostomy tube, with total instillation volume determined on volumetric measurements using pyelography, not to exceed 15 mL (60 mg of mitomycin). The dose is instilled once weekly for 6 weeks. In patients with a complete response 3 months after initiating Jelmyto, therapy can continue once a month for an additional 11 instillations.

Guidelines
The National Comprehensive Cancer Network (NCCN) guidelines for **bladder cancer** (version 2.2023 – April 25, 2023) recommend Jelmyto as a primary treatment for upper urinary tract tumors (category 2A).[2,3] Jelmyto is recommended following complete or near complete endoscopic resection or ablation of a non-metastatic, residual, low-grade, low volume, solitary tumor in patients who are not a candidate for or are not seeking definitive treatment with nephroureterectomy.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Jelmyto. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Jelmyto as well as the monitoring required for adverse events and long-term efficacy, approval requires Jelmyto to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Jelmyto is recommended in those who meet the following criteria:

FDA-Approved Indication

97. Upper Tract Urothelial Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has non-metastatic disease; AND
- **C)** Patient has low-grade disease; AND
- **D)** Patient has undergone endoscopic resection or ablation; AND
- **E)** Jelmyto is prescribed by or in consultation with an oncologist or urologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Jelmyto is not recommended in the following situations.

337. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1080. Jelmyto® for pyelocalyceal solution [prescribing information]. Princeton, NJ: UroGen Pharma; September 2022.

1081. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 5, 2023.

1082. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 5, 2023. Search term: Jelmyto.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Other) – Valrubicin Products Prior Authorization Policy
- Valstar® (valrubicin intravesical solution– Endo, generic)

REVIEW DATE: 12/13/2023

OVERVIEW

Valrubicin, an anthracycline topoisomerase inhibitor, is indicated for intravesical therapy of BCG-refractory **carcinoma *in situ* (CIS) of the urinary bladder** in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality.[1]

Guidelines

The National Comprehensive Cancer Network guidelines for **bladder cancer** (version 3.2023 – May 25, 2023) recommend intravesical valrubicin in the event of a Bacillus Calmette-Guerin (BCG) shortage and for BCG-refractory carcinoma *in situ* (Tis) disease as either initial therapy if high risk and BCG unresponsive or intolerant, or for refractory or persistent disease.[2,3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of valrubicin. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with valrubicin as well as the monitoring required for adverse events and long-term efficacy, approval requires valrubicin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of valrubicin is recommended in those who meet the following criteria:

FDA-Approved Indication

98. Bladder Cancer. Approve for 2 months if the patient meets the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets one of the following (i, ii, or ii):
  - **i.** Patient has Bacillus Calmette-Guerin (BCG)-refractory carcinoma; OR
  - **ii.** Patient is intolerant of Bacillus Calmette-Guerin (BCG); OR
  - **iii.** According to the prescriber, valrubicin will be used due to a Bacillus Calmette-Guerin (BCG) shortage; AND
- **C)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of valrubicin is not recommended in the following situations:

338. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1083. Valstar solution [prescribing information]. Malvern, PA: Endo Pharmaceuticals Solutions; October 2019.

1084. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 11, 2023. Search term: valrubicin.

1085. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – May 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 11, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Abiraterone Acetate Prior Authorization Policy
- Abiraterone Acetate (Zytiga® tablets – Janssen Biotech, generic)

REVIEW DATE: 12/20/2023

OVERVIEW

Abiraterone acetate, an androgen biosynthesis inhibitor, is indicated for following uses in combination with prednisone:[1]

- **Metastatic castration-resistant prostate cancer**.
- **Metastatic castration-sensitive prostate cancer**, high-risk.

Guidelines

Abiraterone acetate is addressed in National Comprehensive Cancer Network (NCCN) prostate cancer guidelines (version 4.2023 – September 7, 2023) in a variety of clinical settings:

- For initial therapy for patients in the very-high-risk group, abiraterone acetate + prednisone + external beam radiation therapy (EBRT) and 2 years of androgen deprivation therapy (ADT) if the life expectancy is > 5 years or the patient is symptomatic is recommended (category 2A).
- For initial therapy for patients classified in the regional risk group (metastases in regional nodes [N1] with no distant metastases [M0]) and with a > 5 year expected patient survival or symptomatic, preferred therapy is EBRT + ADT + abiraterone acetate + prednisone (category 2A). ADT (without EBRT) ± abiraterone + prednisone is also recommended in this setting (category 2A). Abiraterone + ADT should be considered for a total of 2 years for those patients with N1 disease who are treated with radiation to the prostate and pelvic nodes. ADT in this setting includes orchiectomy, gonadotropin-releasing hormone (GnRH), or degarelix.
- For patients who are positive for distant metastasis (M1) and have castration-naïve disease, ADT + abiraterone + prednisone is a preferred recommendation (category 1).
- For patients with M0, prostate specific antigen (PSA) persistence or recurrence after radical prostatectomy with pelvic recurrence and life expectancy > 5 years, abiraterone + prednisone + ADT is recommended (category 2A). PSA persistence/recurrence after radical prostatectomy is defined as failure of PSA to fall to undetectable levels (PSA persistence) or undetectable PSA after radical prostatectomy with a subsequent detectable PSA that increases on 2 or more determinations (PSA recurrence) or that increases to PSA > 0.1 ng/mL.
- For patients who progress to castration-resistant prostate cancer (CRPC) and are positive for distant metastasis (M1) with no visceral metastases, abiraterone + prednisone is a preferred regimen (category 1) for patients who have not received prior novel hormone therapy (category 1). For patients who have received prior novel hormone therapy, abiraterone + prednisone is recommended (category 2A); abiraterone +dexamethasone is recommended in this setting for patients who have not received docetaxel if patients have had disease progression on either formulation of abiraterone (category 2A). For BRCA mutation-positive metastatic CRPC, abiraterone in combination with Lynparza® (olaparib tablets) or Zejula® (niraparib capsules) are both category 1 recommended therapies listed as "useful in certain circumstances" if patient had no prior docetaxel or no prior novel hormone therapy. It is a category 2A recommendation if patients had prior docetaxel and no prior novel hormone therapy. Abiraterone + Zejula is a category 2B recommendation for prior novel hormone therapy and no prior docetaxel therapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of abiraterone acetate. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of abiraterone acetate is recommended in those who meet one of the following criteria:

FDA-Approved Indication

4. Prostate Cancer – Metastatic, Castration-Resistant. Approve for 1 year if the patient meets the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The medication is used in combination with prednisone or dexamethasone; AND
- **C)** Patient meets ONE of the following (i, ii, or iii):
  - **i.** The medication is concurrently used with a gonadotropin-releasing hormone (GnRH) agonist; OR

    149. Note: Examples of GnRH agonists include: leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Vantas (histrelin acetate subcutaneous implant).
  - **ii.** The medication is concurrently used with Firmagon (degarelix subcutaneous injection); OR
  - **iii.** Patient has had a bilateral orchiectomy.

150.

2. Prostate Cancer – Metastatic, Castration-Sensitive. Approve for 1 year if the patient meets the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The medication is used in combination with prednisone; AND
- **C)** Patient meets ONE of the following (i, ii, or iii):
  - **i.** The medication is concurrently used with a gonadotropin-releasing hormone (GnRH) agonist OR

    151. Note: Examples of GnRH agonists include: leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Vantas (histrelin acetate subcutaneous implant).
  - **ii.** The medication is concurrently used with Firmagon (degarelix subcutaneous injection); OR
  - **iii.** Patient has had a bilateral orchiectomy.

Other Uses with Supportive Evidence

3. Prostate Cancer – Radical Prostatectomy. Approve for 1 year if the patient meets all of the following (A, B, C, D, and E):

a. Patient is ≥ 18 years of age; AND
b. The medication is used in combination with prednisone; AND
c. Patient has prostate specific antigen (PSA) persistence or recurrence following radical prostatectomy; AND
d. Patient has pelvic recurrence; AND
e. Patient meets one of the following (i, ii, or iii):

i. The medication is concurrently used with gonadotropin-releasing hormone (GnRH) agonist; OR

152. Note: Examples of GnRH agonists include: leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Vantas (histrelin acetate subcutaneous implant).

ii. The medication is used in combination with Firmagon (degarelix subcutaneous injection); OR

iii. Patient has had a bilateral orchiectomy.

4. **Prostate Cancer – Regional Risk Group.** Approve for 1 year if the patient meets all of the following (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** The medication is used in combination with prednisone; AND
   - **C)** Patient has regional lymph node metastases and no distant metastases; AND
   - **D)** Patient meets one of the following (i, ii, or iii):
     - **i.** The medication is concurrently used with gonadotropin-releasing hormone (GnRH) agonist; OR

       153. Note: Examples of GnRH agonists include: leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Vantas (histrelin acetate subcutaneous implant).
     - **ii.** The medication is used in combination with Firmagon (degarelix subcutaneous injection); OR
     - **iii.** Patient has had a bilateral orchiectomy.

5. **Prostate Cancer – Very-High-Risk Group**. Approve for 2 years (total) if the patient meets all of the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** The medication is used in combination with prednisone; AND
   - **C)** According the prescriber, the patient is in the very-high-risk group; AND

     154. Note: Very-high-risk group includes patients who have one of the following: primary Gleason pattern 5; 2 or 3 high-risk features; > 4 cores with Grade Group 4 or 5; tumor that invades seminal vesicles; tumor that is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall.
   - **D)** The medication is used in combination with external beam radiation therapy; AND
   - **E)** Patient meets one of the following (i, ii, or ii):
     - **i.** The medication is concurrently used with gonadotropin-releasing hormone (GnRH) agonist; OR

       155. Note: Examples of GnRH agonists include: leuprolide injection, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Vantas (histrelin acetate subcutaneous implant).
     - **ii.** The medication is used in combination with Firmagon (degarelix subcutaneous injection); OR
     - **iii.** Patient has had a bilateral orchiectomy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of abiraterone acetate is not recommended in the following situations:

156. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Zytiga® tablets [prescribing information]. Horsham, PA: Janssen Biotech; August 2021.
2. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – September 7, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed December 17, 2023.
3. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed December 17, 2023. Search term: abiraterone acetate.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Akeega Prior Authorization Policy
- Akeega™ (niraparib and abiraterone acetate tablets – Janssen Biotech)

REVIEW DATE: 08/30/2023

OVERVIEW
Akeega is a combination of niraparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, and abiraterone acetate, a cytochrome P450 (CYP)17 inhibitor, indicated with prednisone for the treatment of deleterious or suspected deleterious BReast CAncer (BRCA)-mutated **(BRCAm**) **metastatic castration-resistant prostate cancer** (mCRPC) in adults.[1]

GUIDELINES
National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (version 3.2023 – August 7, 2023) do not include Akeega yet.[2] In the first-line setting for mCRPC, the "preferred" regimens are abiraterone, docetaxel, or Xtandi® (enzalutamide tablets and capsules) [all category 1]; the following regimens are listed as "useful in certain circumstances": Lynparza® (olaparib tablets) + abiraterone for patients with *BRCA*m (category 1) and Talzenna® (talazoparib capsules) + Xtandi for patients with *HRR*m (category 1).

POLICY STATEMENT
90. Prior Authorization is recommended for prescription benefit coverage of Akeega. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Akeega is recommended in those who meet the following criteria:

FDA-Approved Indication
-

1. Prostate Cancer. Approve for 1 year if the patient meets the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has metastatic castration-resistant prostate cancer; AND
- **C)** Patient has a BReast CAncer (*BRCA)* mutation; AND
- **D)** The medication is used in combination with prednisone; AND
- **E)** Patient meets one of the following (i or ii):
  - **i.** The medication is used concurrently with a gonadotropin-releasing hormone (GnRH) analog; OR
    - Note: Examples are leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Vantas (histrelin acetate subcutaneous implant), Firmagon (degarelix acetate subcutaneous injection), and Orgovyx (relugolix tablets).
  - **ii.** Patient has had a bilateral orchiectomy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Akeega is not recommended in the following situations:

157. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

459. Akeega™ tablets [prescribing information]. Horsham, PA: Janssen; August 2023.
460. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – August 7, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on August 17, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Alecensa Prior Authorization Policy
- Alecensa® (alectinib capsules – Genentech)

REVIEW DATE: 01/11/2023

OVERVIEW

Alecensa, a tyrosine kinase inhibitor, is indicated for the treatment of patients with anaplastic lymphoma kinase (*ALK*)-positive, metastatic **non-small cell lung cancer (NSCLC)**, as detected by an FDA-approved test.[1]

GUIDELINES

Alecensa has been addressed in National Comprehensive Cancer Network (NCCN) guidelines:[2]

- **Histiocytic Neoplasms:** Guidelines (version 1.2022 – May 20, 2022) recommend Alecensa as a "useful in certain circumstances" treatment option for *ALK*-positive Erdheim-Chester Disease (category 2A).[3]
- **Non-Small Cell Lung Cancer:** Guidelines (version 1.2023 – December 22, 2022) recommend testing for *ALK* rearrangements in eligible patients with NSCLC.[4] If *ALK* rearrangement is discovered prior to first-line systemic therapy, Alecensa is a preferred first-line treatment option (category 1). If *ALK* rearrangement is discovered during first-line systemic therapy, options are to complete the planned systemic therapy (including maintenance therapy) or to interrupt the systemic therapy and treat with Alecensa (preferred, category 2A) or another ALK inhibitor. NCCN recommendations for patients with disease progression often include continuing the first-line targeted therapy, depending on type of progression.
- **T-Cell Lymphomas:** Guidelines (version 1.2023 – January 5, 2023) recommend Alecensa as a treatment option for patients with relapsed or refractory *ALK*-positive anaplastic large cell lymphoma (ALCL).[5] NCCN notes a phase II study involving patients ≥ 6 years of age with relapsed or refractory *ALK*-positive ALCL. However, this was a small study involving 10 patients with a median age of 19.5 years.
- **Uterine Neoplasms:** Guidelines (version 1.2023 – December 22, 2022) recommend Alecensa as a treatment option for patients with inflammatory myofibroblastic tumor with *ALK* translocation (category 2A).[6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Alecensa. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Alecensa is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. **Non-Small Cell Lung Cancer.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has advanced or metastatic disease; AND
   - **C)** Patient has anaplastic lymphoma kinase (*ALK*)-positive disease; AND
   - **D)** The mutation was detected by an approved test.

Other Uses with Supportive Evidence

2. **Anaplastic Large Cell Lymphoma.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has anaplastic lymphoma kinase (*ALK*)-positive disease; AND
   - **C)** Patient meets one of the following criteria (i or ii):
     - **i.** Patient has relapsed disease; OR
     - **ii.** Patient has refractory disease.

3. **Erdheim-Chester Disease.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has anaplastic lymphoma kinase (*ALK*) rearrangement/fusion-positive disease.

4. **Inflammatory Myofibroblastic Tumor.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has anaplastic lymphoma kinase (*ALK*)-positive disease; AND
   - **C)** Patient meets one of the following criteria (i or ii):
     - **i.** Patient has advanced, recurrent, or metastatic disease; OR
     - **ii.** The tumor is inoperable.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Alecensa is not recommended in the following situations:

158. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

461. Alecensa® capsules [prescribing information]. South San Francisco, CA: Genentech; September 2021.
462. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 10, 2023. Search term: alectinib.
463. The NCCN Histiocytic Neoplasms Clinical Practice Guidelines in Oncology (version 1.2022 – May 20, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 9, 2023.
464. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 9, 2023.
465. The NCCN T-Cell Lymphoma Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 9, 2023.
466. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 9, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Alunbrig Prior Authorization Policy
- Alunbrig® (brigatinib tablets – ARIAD/Takeda)

467.
REVIEW DATE: 07/12/2023

OVERVIEW
Alunbrig, a kinase inhibitor, is indicated for the treatment of adults with anaplastic lymphoma kinase (ALK)-positive, metastatic **non-small cell lung cancer (NSCLC)** as detected by an FDA-approved test.[1]

Guidelines
Alunbrig is addressed in National Comprehensive Cancer Network (NCCN) guidelines:[2-5]
- **Histiocytic Neoplasms:** Guidelines (version 1.2022 – May 20, 2022) recommend Alunbrig as a "useful in certain circumstances" treatment option for *ALK*-positive Erdheim-Chester disease (category 2A).[3]
- **Inflammatory Myofibroblastic Tumor (IMT):** NCCN Soft Tissue Sarcoma guidelines (version 2.2023 – April 25, 2023) and NCCN Uterine Neoplasms guidelines (version 2.2023 – April 28, 2023) recommend Alunbrig as a treatment option for IMT with *ALK* translocation.[5,6]
- **NSCLC:** Guidelines (version 3.2023 – April 13, 2023) recommend testing for *ALK* rearrangements in eligible patients with NSCLC.[4] If *ALK* rearrangement is discovered prior to first-line systemic therapy, Alunbrig is a preferred first-line treatment option (category 1). If *ALK* rearrangement is discovered during first-line systemic therapy, options are to complete the planned systemic therapy (including maintenance therapy) or to interrupt the systemic therapy and treat with Alunbrig ("preferred", category 2A) or another ALK inhibitor. NCCN recommendations for patients with disease progression often include continuing the first-line targeted therapy, depending on type of progression.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Alunbrig. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Alunbrig is recommended in those who meet one of the following criteria:

FDA-Approved Indication

71. Non-Small Cell Lung Cancer. Approve for 1 year if the patients meets the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has advanced or metastatic disease; AND
- **C)** Patient has anaplastic lymphoma kinase (*ALK*)-positive disease; AND
- **D)** The mutation was detected by an approved test.

Other Uses with Supportive Evidence

2. **Erdheim-Chester Disease.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has anaplastic lymphoma kinase (*ALK*) rearrangement/fusion-positive disease.
   468.
3. **Inflammatory Myofibroblastic Tumor.** Approve for 1 year if the patients meets the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has anaplastic lymphoma kinase (*ALK*)-positive disease;
   C) Patient meets one of the following (i or ii):
      i. Patient has advanced, recurrent, or metastatic disease; OR
      ii. The tumor is inoperable.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Alunbrig is not recommended in the following situations:

159. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

469. Alunbrig® tablets [prescribing information]. Cambridge, MA: ARIAD/Takeda; February 2022.
2. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 3, 2023. Search terms: brigatinib.
3. The NCCN Histiocytic Neoplasms Clinical Practice Guidelines in Oncology (version 1.2022 – May 20, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 3, 2023.
4. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – April 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 3, 2023.
5. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 3, 2023.
6. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (version 2.2023 – April 28, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 3, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Augtyro Prior Authorization Policy
- Augtyro™ (repotrectinib capsules – Bristol-Myers Squibb Company)

REVIEW DATE: 11/29/2023

OVERVIEW
Augtyro, a kinase inhibitor, is indicated for the treatment of locally advanced or metastatic ***ROS1*-positive** non-small cell lung cancer **(NSCLC)** in adults.[1]

Guidelines
The National Comprehensive Cancer Network (NCCN) NSCLC guidelines (version 1.2024 – December 21, 2023) recommend Augtyro, Rozlytrek® (entrectinib capsules and oral pellets), and Xalkori® (crizotinib capsules) as "Preferred" first-line treatment options (all category 2A) for patients with *ROS1* rearrangement-positive NSCLC.[2] Zykadia® (ceritinib capsules and tablets) is also an option under "Other Recommended" therapy (category 2A) in the first-line setting.

POLICY STATEMENT
91. Prior Authorization is recommended for prescription benefit coverage of Augtyro. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Augtyro is recommended in those who meet the following criteria:

FDA-Approved Indication

3. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has locally advanced or metastatic disease; AND
- **C)** Patient has *ROS1*-positive non-small cell lung cancer; AND
- **D)** The mutation was detected by an approved test.

ZZZZ)
CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Augtyro is not recommended in the following situations:

160. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

310. Augtyro™ capsules [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; November 2023.
311. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 1.2024 – December 21, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 5, 2024.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Ayvakit Prior Authorization Policy
- Ayvakit™ (avapritinib tablets – Blueprint Medicines)

REVIEW DATE: 05/31/2023

OVERVIEW

Ayvakit, a kinase inhibitor, is indicated for the following uses in adults:[1]

- **Gastrointestinal stromal tumor (GIST),** unresectable or metastatic, harboring a platelet-derived growth factor receptor alpha (*PDGFRA*) exon 18 mutation, including *PDGFRA* D842V mutations. Patients should be selected for treatment with Ayvakit based on the presence of a *PDGFRA* exon 18 mutation; an FDA-approved test for the detection of this mutation is not currently available.
- **Advanced systemic mastocytosis,** including patients with aggressive systemic mastocytosis, systemic mastocytosis with an associated hematological neoplasm, and mast cell leukemia. Ayvakit is not recommended for the treatment of patients with advanced systemic mastocytosis with platelet counts of less than 50 x 10^9/L.
- **Indolent systemic mastocytosis**.

A)

Guidelines

Ayvakit is discussed in the guidelines from National Comprehensive Cancer Network (NCCN):[3]

- **GIST:** NCCN guidelines (version 1.2023 – March 13, 2023) note that Ayvakit is one of the primary treatment options for GIST with *PDGFRA* exon 18 mutation, including *PDGFRA* D842V mutations (category 2A).[2] Imatinib is a category 1 recommended option for primary treatment. The guidelines note that most mutations in the *PDGFRA* gene are associated with a response to imatinib, with the notable exception of *PDGFRA* D842V mutation. Ayvakit (for *PDGFRA* exon 18 mutation that is insensitive to imatinib, including the *D842V* mutation) is listed as a preferred regimen for neoadjuvant therapy for resectable GISTs with significant morbidity (category 2A). Ayvakit is listed as an additional option after failure on approved therapies. The approved therapies are imatinib and Ayvakit (for *PDGFRA* mutation) as first-line therapy; sunitinib; or Sprycel® (dasatinib tablets; for *PDGFRA* exon 18 mutations that are insensitive to imatinib [including the *PDGFRA D842V* mutation]) as second-line therapy; Stivarga® (regorafenib tablets) as third-line therapy; and Qinlock® (ripretinib tablets) as fourth-line therapy.
- **Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions:** NCCN guidelines (version 1.2023 – May 19, 2023) note that since Ayvakit targets *PDGFRA* exon 18 mutation, it may have a role for use in patients with *FIP1L1-PDGFRA* positive myeloid/lymphoid neoplasms with eosinophilia harboring *PDGFRA* D842V mutation, which is resistant to imatinib (category 2A).[4] If this mutation is identified, a clinical trial with Ayvakit is preferred (if available), rather than off-label use.
- **Systemic Mastocytosis:** NCCN guidelines (version 1.2023 – May 24, 2023) recommend single-agent Ayvakit if the patient has platelets ≥ 50 x 10^9/L as preferred treatment of aggressive systemic mastocytosis, systemic mastocytosis with an associated neoplasm, and mast cell leukemia with or without an associated hematologic neoplasm (category 2A).[5]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Ayvakit. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Ayvakit is recommended in those who meet one of the following criteria:

FDA-Approved Indications

77. Gastrointestinal Stromal Tumor. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following criteria (i or ii):
  - **i.** The tumor is positive for platelet-derived growth factor receptor alpha (*PDGFRA*) exon 18 mutation; OR
    - **B)** Note: *PDGFRA* exon 18 mutation includes *PDGFRA* D842V mutations.
  - **ii.** Patient has tried each of the following (a, b, c, and d):
    - **a)** Imatinib; AND
    - **b)** One of sunitinib or Sprycel (dasatinib tablets); AND
    - **c)** Stivarga (regorafenib tablets); AND
    - **d)** Qinlock (ripretinib tablets).

78. Systemic Mastocytosis. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has a platelet count ≥ 50 x 10^9/L (≥ 50,000/mcL); AND
- **C)** Patient meets one of the following criteria (i or ii):
  - **i.** Patient has indolent systemic mastocytosis; OR
  - **ii.** Patient has one of the following subtypes of advanced systemic mastocytosis (a, b, or c):
    - **a)** Aggressive systemic mastocytosis; OR
    - **b)** Systemic mastocytosis with an associated hematological neoplasm; OR
    - **c)** Mast cell leukemia.

C)

Other Uses with Supportive Evidence

3. Myeloid/Lymphoid Neoplasms. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has eosinophilia; AND
- **C)** The tumor is positive for platelet-derived growth factor receptor alpha (*PDGFRA*) D842V mutation.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ayvakit is not recommended in the following situations:

12. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

49. Ayvakit™ tablets [prescribing information]. Cambridge, MA: Blueprint Medicines Corporation; May 2023.
50. The NCCN Gastrointestinal Stromal Tumors Clinical Practice Guidelines in Oncology (version 1.2023 – March 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 30, 2023.
51. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 30, 2023. Search term: avapritinib.
52. The NCCN Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase fusion genes Clinical Practice Guidelines in Oncology (version 1.2023 – May 19, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 30, 2023.
53. The NCCN Systemic Mastocytosis Clinical Practice Guidelines in Oncology (version 1.2023 – May 24, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 30, 2023.

D)

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Balversa Prior Authorization Policy
- Balversa® (erdafitinib tablets – Janssen)

REVIEW DATE: 04/12/2023

OVERVIEW

Balversa, a kinase inhibitor, is indicated for the treatment of **locally advanced or metastatic urothelial carcinoma** in adults with susceptible fibroblast growth factor receptor (FGFR)3 or FGFR2 genetic alterations, and progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of adjuvant or neoadjuvant platinum-containing chemotherapy.[1]

Patients are selected for treatment with Balversa based on the presence of susceptible FGFR genetic alterations in tumor specimens detected by an FDA-approved companion diagnostic.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for bladder cancer (version 1.2023 – February 9, 2023) recommend Balversa as a single agent, post-platinum or –checkpoint inhibitor therapy in patients with bladder cancer, upper genitourinary tract tumors, primary carcinoma of the urethra, and urothelial carcinoma of the prostate with susceptible FGFR2 or FGFR3 genetic alterations.[2,3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Balversa. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Balversa is recommended in those who meet the following criteria:

FDA-Approved Indication

99. Urothelial Carcinoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient has locally advanced or metastatic disease; AND
- **B)** Patient has susceptible fibroblast growth factor receptor 3 or fibroblast growth factor receptor 2 genetic alterations; AND
- **C)** Patient has progressed during or following prior platinum-containing chemotherapy or checkpoint inhibitor therapy.

  Note: Examples of platinum-containing chemotherapy include cisplatin and carboplatin. Examples of checkpoint inhibitors include: Keytruda (pembrolizumab intravenous infusion), Opdivo (nivolumab intravenous infusion), Tecentriq (atezolizumab intravenous infusion), Imfinzi (durvalumab intravenous infusion), and Bavencio (avelumab intravenous infusion).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Balversa is not recommended in the following situations:

339. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1086. Balversa® tablets [prescribing information]. Horsham, PA: Janssen; March 2023.
1087. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – February 9, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed April 10, 2023.
1088. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 10, 2023. Search term: erdafitinib.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Bexarotene (Oral) Prior Authorization Policy
- Targretin® (bexarotene capsules – Bausch Health, generic)

REVIEW DATE: 11/22/2023

OVERVIEW

Oral bexarotene is indicated for the treatment of **cutaneous manifestations of cutaneous T-cell lymphoma** in patients who are refractory to at least one prior systemic therapy.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) Primary Cutaneous Lymphomas guidelines (version 1.2023 – January 5, 2023) recommend oral bexarotene as an option for the treatment of cutaneous lymphomas (e.g., mycosis fungoides, Sézary syndrome, anaplastic large cell lymphoma [ALCL], lymphomatoid papulosis), as initial therapy and for relapsed/refractory cases. NCCN notes there are limited data from case reports demonstrating efficacy of oral bexarotene for the treatment of ALCL with multifocal lesions and for lymphomatoid papulosis with extensive lesions.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of bexarotene capsules. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with bexarotene capsules as well as the monitoring required for adverse events and long-term efficacy, approval requires bexarotene capsules to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of bexarotene capsules is recommended in those who meet the following criteria:

FDA-Approved Indication

72. Cutaneous T-Cell Lymphoma. Approve for 1 year if the patient meets the following (A and B):
V) Patient has cutaneous manifestations/lesions; AND
W) The medication is prescribed by or in consultation with an oncologist or a dermatologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of bexarotene capsules is not recommended in the following situations:

161. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

312. Targretin® capsules [prescribing information]. Bridgewater, NJ: Bausch Health; April 2020.
313. The NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 20, 2023.
314. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 20, 2023. Search terms: bexarotene.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Bexarotene (Topical) Prior Authorization Policy
- Targretin® (bexarotene 1% gel – Bausch Health, generic)

REVIEW DATE: 11/22/2023

OVERVIEW

Bexarotene gel is indicated for the topical treatment of cutaneous lesions in patients with **cutaneous T-cell lymphoma** (Stage 1A and 1B) who have refractory or persistent disease after other therapies or who have not tolerated other therapies.[1]

Guidelines

National Comprehensive Cancer Network (NCCN) Primary Cutaneous Lymphomas guidelines (version 1.2023 – January 5, 2023) recommend topical bexarotene as an option for the treatment of cutaneous lymphomas (e.g., mycosis fungoides, Sézary syndrome, T-cell lymphoma), as initial therapy and for relapsed/refractory cases. NCCN notes there are case reports demonstrating efficacy of topical bexarotene in treating primary cutaneous B-cell lymphomas in children. The NCCN T-Cell Lymphomas guidelines (version 1.2023 – January 5, 2023) recommend skin-directed therapies (refers to bexarotene in primary cutaneous lymphomas guidelines) for first-line therapy (category 2A) of chronic/smoldering adult T-cell leukemia/lymphoma subtype.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of bexarotene gel. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with bexarotene gel as well as the monitoring required for adverse events and long-term efficacy, approval requires bexarotene gel to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Bexarotene gel is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Cutaneous T-Cell Lymphoma.** Approve for 1 year if the patient meets the following (A and B):
   73. Patient has cutaneous manifestations/lesions; AND
   74. The medication is prescribed by or in consultation with an oncologist or a dermatologist.

Other Uses with Supportive Evidence

2. **Adult T-Cell Leukemia/Lymphoma.** Approve for 1 year if the patient meets the following (A, B, and C):
   A) Patient has chronic/smoldering subtype; AND
   B) The medication is used as first-line therapy; AND

C) The medication is prescribed by or in consultation with an oncologist or a dermatologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of bexarotene gel is not recommended in the following situations:

162. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

315. Targretin® gel [prescribing information]. Bridgewater, NJ: Bausch Health; February 2020.
316. The NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 20, 2023.
317. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 20, 2023. Search terms: bexarotene gel.
318. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 20, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Bosulif Prior Authorization Policy
- Bosulif® (bosutinib tablets – Pfizer)

REVIEW DATE: 05/31/2023; selected revision 10/04/2023

OVERVIEW

Bosulif, a tyrosine kinase inhibitor (TKI), is indicated for the following uses:[1]

- **Chronic myelogenous leukemia (CML)**, in chronic phase that is Philadelphia chromosome positive (Ph+) that is newly-diagnosed or resistant or intolerant to prior therapy in adults and pediatric patients ≥ 1 year of age.
- **CML**, Ph+, in accelerated, or blast phase, with resistance or intolerance to prior therapy in adults.

Guidelines

Bosulif is addressed in guidelines from National Comprehensive Cancer Network (NCCN):

- **Acute Lymphoblastic Leukemia (ALL):** NCCN guidelines (version 2.2023 – July 28, 2023) recommend Bosulif for Ph+ disease in many different clinical circumstances (e.g., induction, consolidation therapy, maintenance, or relapsed or refractory disease) [category 2A].[2] TKIs in combination with other agents (e.g., chemotherapy or corticosteroids) are recommended for induction therapy for Ph+ ALL. TKIs have also been incorporated into consolidation and maintenance therapy, as well as in the relapsed/refractory setting (category 2A). TKI options include: Bosulif, Sprycel® (dasatinib tablets), imatinib, Tasigna® (nilotinib capsules), or Iclusig® (ponatinib tablets) [category 2A]. NCCN panel notes that not all TKIs have been directly studied within the context of each specific regimen and there are limited data for Bosulif in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance and disease-related features. For adults and adolescents, Iclusig has activity against T315I mutations and/or in whom no other TKI is indicated (category 2A).
- **CML:** NCCN guidelines (version 1.2024 – August 1, 2023) recommend Bosulif as a "preferred" primary regimen for newly diagnosed chronic phase Ph+ CML in patients with a low-, intermediate-, or high-risk score (category 1).[3] Bosulif is also recommended as a "preferred" regimen for patients with advanced phase or blast phase CML (category 2A). Bosulif is also recommended as an alternative TKI treatment (after primary treatment with imatinib, Sprycel, or Tasigna (category 2A). Bosulif is also recommended in a variety of other situations, including post-allogeneic hematopoietic stem cell transplantation (HSCT) [category 2A].
- **Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes:** NCCN guidelines (version 2.2023 – July 14, 2023) recommend Bosulif as "other recommended regimens" for patients with *ABL1* rearrangements (category 2A).[4] It is also recommended as treatment in combination with ALL- or acute myeloid leukemia-type induction chemotherapy followed by allogeneic HSCT (if eligible) for lymphoid, myeloid, or mixed lineage neoplasms with eosinophilia and *ABL1* rearrangement in blast phase (category 2A).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Bosulif. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Bosulif is recommended in those who meet one of the following criteria:

FDA-Approved Indication

75. Chronic Myeloid Leukemia. Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient is ≥ 1 year of age; AND
- **B)** Patient has Philadelphia chromosome-positive chronic myeloid leukemia.

Other Uses with Supportive Evidence

2. Acute Lymphoblastic Leukemia. Approve for 1 year if the patient meets the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has Philadelphia chromosome-positive acute lymphoblastic leukemia; AND
- **C)** Patient has tried at least one other tyrosine kinase inhibitor for Philadelphia chromosome-positive acute lymphoblastic leukemia.
  Note: Examples include imatinib and Sprycel (dasatinib tablets).

2. Myeloid/Lymphoid Neoplasms with Eosinophilia. Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The tumor has an *ABL1* rearrangement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Bosulif is recommended in those who meet the following criteria:

163. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

470. Bosulif® tablets [prescribing information]. New York, NY: Pfizer; September 2023.
471. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 2.2023 – July 28, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 2, 2023.
472. The NCCN Chronic Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 1.2024 – August 1, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 2, 2023.
473. The NCCN Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes Clinical Practice Guidelines in Oncology (version 2.2023 – July 14, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 2, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Braftovi Prior Authorization Policy
- Braftovi® (encorafenib capsules – Array BioPharma)

REVIEW DATE: 07/19/2023; selected revision 10/18/2023

OVERVIEW

Braftovi, a BRAF inhibitor, is indicated for the following uses:[1]

- **Colorectal cancer**, in combination with Erbitux® (cetuximab intravenous infusion), for the treatment of metastatic disease and a *BRAF V600E* mutation, as detected by an FDA-approved test, after prior therapy in adults.
- **Melanoma**, in combination with Mektovi® (binimetinib tablets), for the treatment of unresectable or metastatic disease and a *BRAF V600E* or *V600K* mutation, as detected by an FDA-approved test in adults.
- **Non-small cell lung cancer (NSCLC),** in combination with Mektovi, for the treatment of adult patients with metastatic NSCLC with a *BRAF V600E* mutation, as detected by an FDA-approved test.

It is a limitation of use that Braftovi is not indicated for treatment of patients with wild-type BRAF melanoma, wild-type BRAF colorectal cancer, or wild-type BRAF NSCLC.

Guidelines

National Comprehensive Cancer Network guidelines support use of Braftovi in the following cancers.[5]

- **Colon** and **Rectal Cancer:** Guidelines for colon cancer (version 2.2023 – April 25, 2023) and rectal cancer (version 3.2023 – March 26, 2023) recommend Braftovi for some situations in patients with *BRAF V600E*-mutated disease.[3] For primary treatment (following adjuvant chemotherapy) or as subsequent use, Braftovi + Erbitux or Vectibix® (panitumumab intravenous infusion) is a recommended treatment option.
- **Melanoma, Cutaneous:** Guidelines (version 2.2023 – March 10, 2023) recommend BRAF/MEK inhibitor combinations among the preferred therapies for first-line and subsequent treatment of metastatic or unresectable melanoma with a *V600*-activating mutation.[2] The combinations are also recommended for adjuvant treatment (category 2B). While combination BRAF/MEK inhibition is preferred, if a combination is contraindicated, monotherapy with a BRAF inhibitor (Tafinlar® [dabrafenib capsules] or Zelboraf® [vemurafenib tablets]) is a recommended option, especially in patients who are not appropriate candidates for checkpoint immunotherapy.
- **Non-Small Cell Lung Cancer:** Guidelines (version 3.2023 – April 13, 2023) recommend Tafinlar + Mekinist® (trametinib tablets) for first-line "preferred" and subsequent therapy (both category 2A) for *BRAF V600E* mutation-positive disease.[6] Zelboraf or Tafinlar monotherapy is also recommended under "useful in certain circumstances" (both category 2A). Braftovi + Mektovi combination is not yet addressed in the guidelines.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Braftovi. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Braftovi is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Colon or Rectal Cancer.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   62. Patient is ≥ 18 years of age; AND
   63. Patient has *BRAF V600E* mutation-positive disease; AND
   64. Patient has previously received a chemotherapy regimen for colon or rectal cancer; AND

- Note: Examples of chemotherapy regimens include a fluoropyrimidine such as 5-fluorouracil (5-FU), capecitabine; oxaliplatin, irinotecan, or an adjunctive chemotherapy regimen such as FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).

   65. The medication is prescribed as part of a combination regimen for colon or rectal cancer.

- Note: Examples of combination regimens include Braftovi + Erbitux (cetuximab intravenous infusion), Braftovi + Vectibix (panitumumab intravenous infusion).
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2. **Melanoma.** Approve for 1 year if the patient meets the following (A, B, and C):

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has unresectable, advanced, or metastatic melanoma; AND
  - **C)** Patient has *BRAF V600* mutation-positive disease.
  -
  - **3. Non-Small Cell Lung Cancer.** Approve for 1 year if the patient meets the following (A, B, and C):
    - **A)** Patient is ≥ 18 years of age; AND
    - **B)** Patient has *BRAF V600E* mutation-positive metastatic disease; AND
    - **C)** The medication will be taken in combination with Mektovi (binimetinib tablets).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Braftovi is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

474. Braftovi® capsules [prescribing information]. Boulder, CO: Array BioPharma; October 2023.
475. The NCCN Melanoma Clinical Practice Guidelines in Oncology (version 2.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on July 10, 2023.
476. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on July 10, 2023.
477. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – May 26, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on July 10, 2023.
478. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 10, 2023. Search terms: encorafenib.
479. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – April 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on October 16, 2023.

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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Brukinsa Prior Authorization Policy
- Brukinsa® (zanubrutinib capsules – BeiGene)

REVIEW DATE: 04/19/2023

OVERVIEW

Brukinsa, a Bruton's tyrosine kinase inhibitor (BTK), is indicated for the treatment of the following conditions:[1]

- **Chronic lymphocytic leukemia or small lymphocytic lymphoma,** in adults.
- **Mantle cell lymphoma,** in adults who have received at least one prior therapy.
  - **Marginal zone lymphoma**, relapsed or refractory, in adults who have received at least one anti-CD20-based regimen.
- **Waldenström's Macroglobulinemia,** in adults.

Guidelines

Brukinsa is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):[4]

- **B-Cell Lymphomas**: NCCN guidelines (version 2.2023 – February 8, 2023) address marginal zone lymphoma and mantle cell lymphoma.[2] The guidelines recommend Brukinsa as a "Preferred Regimen" among several as second-line and subsequent therapy for marginal zone lymphoma for patients who have relapsed/refractory disease after at least one prior anti-CD20 monoclonal antibody (mAB)-based regimen (category 2A). For mantle cell lymphoma, Brukinsa is a "Preferred Regimen" for second-line or subsequent therapy (category 2A). There is a footnote that states that Brukinsa or Calquence has not been shown to be effective for Imbruvica-refractory mantle cell lymphoma with *BTK* C481S mutations. Patients with Imbruvica intolerance have been successfully treated with Brukinsa or Calquence without recurrence of symptoms.
- **Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma:** NCCN guidelines (version 2.2023 – January 25, 2023) recommend single-agent Brukinsa as first-line "Preferred Regimen" for patients without 17p deletion/TP53 mutation (category 1) and with 17p deletion/TP53 mutation (category 2A). Brukinsa is also recommended as second-line and subsequent therapy "Preferred Regimen" for patients with or without 17p deletion/TP53 mutation (category 1).[3] In the second-line and subsequent therapy setting, there is a footnote, which states that Brukinsa or Calquence have not been shown to be effective for Imbruvica-refractory chronic lymphocytic leukemia with BTK C481S mutations. Patients with Imbruvica intolerance have been successfully treated with Brukinsa or Calquence without recurrence of symptoms.
- **Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma**: NCCN guidelines (version 1.2023 – July 6, 2022) recommend single-agent Brukinsa as a primary "Preferred Therapy" (category 1).[5] The guidelines also recommend Brukinsa as a "Preferred Therapy" option for previously treated disease (category 1). Brukinsa is also recommended for symptomatic management of Bing Neel Syndrome as a "Preferred Regimen" (category 2A).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Brukinsa. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Brukinsa is recommended in those who meet one of the following criteria:

FDA-Approved Indications

100. Chronic Lymphocytic Leukemia. Approve for 1 year if the patient is ≥ 18 years of age.

101. Mantle Cell Lymphoma. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient is ≥ 18 years of age; AND

B) Patient meets one of the following criteria (i or ii):

i. Patient has tried at least one systemic regimen; OR

Note: Examples of a systemic regimen contain one or more of the following products: rituximab, dexamethasone, cytarabine, carboplatin, cisplastin, oxaliplatin, cyclophosphamide, doxorubicin, vincristine, prednisone, methotrexate, bendamustine, bortezomib, lenalidomide

ii. According to the prescriber, patient is not a candidate for a systemic regimen (i.e., an elderly patients who is frail).

102. Marginal Zone Lymphoma. Approve for 1 year if the patient meets the following criteria (A and B):

92. Note: Marginal zone lymphoma includes gastric MALT lymphoma, non-gastric MALT lymphoma, nodal marginal zone lymphoma, and splenic marginal zone lymphoma.

A) Patient is ≥ 18 years of age; AND

B) Patient has tried at least one systemic regimen.

Note: Examples of a systemic regimen contain one or more of the following products: bendamustine, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, lenalidomide, Gazyva (obinutuzumab intravenous infusion) or Imbruvica (ibrutinib tablets and capsules).

103. Small Lymphocytic Lymphoma. Approve for 1 year if the patient is ≥ 18 years of age.

104. Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma. Approve for 1 year if the patient is ≥ 18 years of age.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Brukinsa is not recommended in the following situations:

164. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

319. Brukinsa™ capsules [prescribing information]. San Mateo, CA: BeiGene; January 2023.
320. The NCCN B-Cell Lymphomas Guidelines in Oncology (version 2.2023 – February 8, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 12, 2023.
321. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (version 2.2023 – January 25, 2023). © 2023 National Comprehensive Cancer Network. Available at http://www.nccn.org. Accessed on April 12, 2023.
322. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed April 12, 2023. Search term: zanubrutinib.
323. The NCCN Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma Clinical Practice Guidelines in Oncology (version 1.2023 – July 6, 2022). © 2022 National Comprehensive Cancer Network. Available at http://www.nccn.org. Accessed on April 12, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Cabometyx Prior Authorization Policy
- Cabometyx® (cabozantinib tablets – Exelixis)

REVIEW DATE: 03/22/2023

OVERVIEW

Cabometyx, a kinase inhibitor, is indicated for the following uses:[1]

- **Differentiated thyroid cancer**, for the treatment of patients ≥ 12 years of age with locally advanced or metastatic disease that has progressed following prior vascular endothelial growth factor receptor (VEGFR)-targeted therapy and who are radioactive iodine-refractory or ineligible.
- **Hepatocellular carcinoma,** for the treatment of patients who have been previously treated with sorafenib.
- **Renal cell carcinoma**, advanced, as monotherapy or in combination with Opdivo® (nivolumab intravenous infusion) as first-line treatment.

Guidelines

Cabometyx is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):[2]

- **Bone cancer:** NCCN guidelines (version 2.2023 – September 28, 2022) recommend Cabometyx as one of the "other recommended regimens" for second-line (relapsed/refractory or metastatic disease) for Ewing sarcoma and osteosarcoma (category 2A).[3]
- **Gastrointestinal stromal tumors:** NCCN guidelines (version 1.2023 – March 13, 2023) recommend Cabometyx as one of the options after progression on approved therapies as "useful in certain circumstances" (category 2A).[2,4] The approved therapies are imatinib and Ayvakit® (avapritinib tablets; for *PDGFRA* mutation) as first-line therapy; sunitinib or Sprycel® (dasatinib tablets; for *PDGFRA* exon 18 mutations that are insensitive to imatinib [including the *PDGFRA D842V* mutation) as second-line therapy; Stivarga® (regorafenib tablets) as third-line therapy; and Qinlock® (ripretinib tablets) as fourth-line therapy.[4]
- **Hepatocellular carcinoma:** NCCN guidelines (version 1.2023 – March 10, 2023) recommend Cabometyx (Child-Pugh Class A only; Category 1) as a subsequent therapy option, along with many other agents.[5]
- **Kidney cancer:** NCCN guidelines (version 4.2023 – January 18, 2023) state that the "preferred regimens" for first-line therapy in favorable risk patients with relapsed or Stage IV renal cell carcinoma (RCC) with predominant clear cell histology are: Inlyta® (axitinib tablets) + Keytruda® (pembrolizumab intravenous infusion), Cabometyx + Opdivo, Lenvima® (lenvatinib capsules) + Keytruda (all category 1). Cabometyx (category 2B) is one of the "other recommended regimens" in this setting.[6] For patients in the poor/intermediate risk grouping, the "preferred regimens" are Inlyta + Keytruda; Cabometyx + Opdivo; Yervoy (ipilimumab intravenous infusion) + Opdivo; Lenvima + Keytruda (all category 1); Cabometyx monotherapy is also recommended (category 2A). Subsequent therapy is categorized based on prior immune-oncology (IO) therapy status. There are no preferred regimens. Cabometyx is listed under "other recommended regimens" for both IO therapy naïve and with prior IO therapy; Cabometyx + Opdivo is also an option (both category 2A). For patients with non-clear cell histology RCC, sunitinib, Cabometyx, and enrollment in clinical trials are noted as preferred therapies (category 2A, preferred); Keytruda, Opdivo, Opdivo + Cabometyx, and Lenvima + everolimus are other recommended regimens (all category 2A). Many other agents are listed as "useful in certain circumstances".

- **Non-small cell lung cancer:** NCCN guidelines (version 2.2023 – February 17, 2023) recommend Cabometyx for *RET* rearrangement positive tumors (category 2A).[7]
- **Uterine neoplasms:** NCCN guidelines (version 1.2023 – December 22, 2022) recommend Cabometyx as one of the other recommended regimens for second or subsequent line of therapy for recurrent endometrial carcinoma (category 2A).[8]
- **Thyroid carcinoma**: NCCN guidelines (version 3.2022 – November 1, 2022) state that Cabometyx can be considered if patient has progression after Lenvima or sorafenib for the treatment of locally recurrent, advanced, and/or metastatic disease that is not amendable to radioactive iodine therapy. This recommendation is for follicular, Hürthle cell, and papillary cancer subtypes (all category 1).[9]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cabometyx. All approvals are provided for 1 year in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cabometyx is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Hepatocellular Carcinoma.** Approve for 1 year if the patient meets the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has been previously treated with at least one systemic regimen.
   324. Note: Examples of a systemic regimen include one of the following drugs: Tecentriq (atezolizumab intravenous infusion), bevacizumab, Imjudo (tremelimumab intravenous infusion), Imfinzi (durvalumab intravenous infusion), sorafenib, Lenvima (lenvatinib capsules), or Opdivo (nivolumab intravenous infusion).

2. **Renal Cell Carcinoma.** Approve for 1 year if the patient meets both of the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has relapsed or stage IV disease.

325.

3. **Thyroid Carcinoma, Differentiated.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   A) Patient is ≥ 12 years of age; AND
   B) Patient has differentiated thyroid carcinoma; AND
   Note: Examples of differentiated thyroid carcinoma include papillary, follicular, and Hürthle cell thyroid carcinoma.
   C) Patient is refractory to radioactive iodine therapy; AND
   D) Patient has tried Lenvima (lenvatinib capsules) or sorafenib.

Other Uses with Supportive Evidence

4. **Bone Cancer.** Approve for 1 year if the patient meets the following criteria (A and B):
   A) Patient meets ONE of the following (i or ii):

326. **i.** Patient has Ewing sarcoma; OR
327. **ii.** Patient has osteosarcoma; AND

B) Patient has tried at least one previous systemic regimen.

328. Note: Examples of a systemic regimen include one of the following: vincristine, doxorubicin, cyclophosphamide, topotecan, irinotecan, cisplatin, ifosfamide, Stivarga (regorafenib tablets), sorafenib.

329.

5. Endometrial Carcinoma. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient is ≥ 18 years of age; AND

B) Patient has tried one systemic regimen.

330. Note: Examples of a systemic regimen include one of the following: carboplatin, paclitaxel, trastuzumab, docetaxel, doxorubicin, cisplatin, and topotecan.

331.

6. Gastrointestinal Stromal Tumors. Approve for 1 year if the patient meets the following (A and B):

A) Patient is ≥ 18 years of age; AND

B) Patient has tried each of the following (i, ii, iii, and iv):

i. One of imatinib or Ayvakit (avapritinib tablets); AND
ii. One of sunitinib or Sprycel (dasatinib tablets); AND
iii. Stivarga (regorafenib tablets); AND
iv. Qinlock (ripretinib tablets).

7. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient is ≥ 18 years of age; AND

B) Patient has a *RET* rearrangement positive tumor.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cabometyx is not recommended in the following situations:

1. **Metastatic Castration-Resistant Prostate Cancer (mCRPC).** Results from the COMET-1 Phase III pivotal study with Cabometyx 60 mg tablets in men with mCRPC are published.[10] Patients included in the study had disease progression after treatment with docetaxel as well as abiraterone acetate and/or Xtandi® (enzalutamide capsules). The study failed to meet its primary endpoint of demonstrating statistically significant increase in overall survival (OS) compared with prednisone. The median OS with Cabometyx was 11.0 months vs. 9.8 months with prednisone, which was not statistically significant. Based on these results, the second Phase III study, COMET-2 has been discontinued.[11] In another small phase 1/2 study (n = 13), treatment with cabozantinib + docetaxel + prednisone vs. docetaxel + prednisone alone improved the median time to progression and overall survival.[13] There is an ongoing Phase III, randomized, open-label study (CONTACT-02) of cabozantinib + Tecentriq (atezolizumab for intravenous injection) in various tumor types, including CRPC.[12]

332.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

333.

334.

REFERENCES

335. Cabometyx® tablets [prescribing information]. San Francisco, CA: Exelixis; September 2021.
336. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 13, 2023. Search term: cabozantinib.

337. The NCCN Bone Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – September 28, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 17, 2023.
338. The NCCN Gastrointestinal Stromal Tumors (GISTs) Clinical Practice Guidelines in Oncology (version 1.2023 – March 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 17, 2023.
339. The NCCN Hepatocellular Carcinoma Clinical Practice Guidelines in Oncology (version 1.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 16, 2023.
340. The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – January 18, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 16, 2023.
341. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – February 17, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 17, 2023.
342. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 16, 2023.
343. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (version 3.2022 – November 1, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 16, 2023.
344. Smith M, De Bono J, Sternberg C, et al. Phase III study of cabozantinib in previously treated metastatic castration-resistant prostate cancer: COMET-1. *J Clin Oncol*. 2016;34:3005-3013.
345. Exelixis. Study of cabozantinib (XL184) versus mitoxantrone plus prednisone in men with previously treated symptomatic castration-resistant prostate cancer (COMET-2). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2017 April 18]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01522443?term=NCT01522443&rank=1. NLM identifier: NCT01522443 (terminated).
346. Exelixis. Study of cabozantinib in combination with atezolizumab to subjects with locally advanced or metastatic solid tumors. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2023 March 20]. Available from: https://clinicaltrials.gov/ct2/show/NCT03170960. NLM identifier: NCT03170960.
347. Madan RA, Karzai FH, Al Harthy M, et al. Cabozantinib plus docetaxel and prednisone in metastatic castration-resistant prostate cancer. *BJU Int*. 2021;127(4):435-444.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Calquence Prior Authorization Policy
- Calquence® (acalabrutinib capsules and tablets – AstraZeneca)

REVIEW DATE: 07/12/2023

OVERVIEW

Calquence, a Bruton's tyrosine kinase (BTK) inhibitor, is indicated in adults for the following uses:[1,2]

- **Chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL)**.
- **Mantle cell lymphoma**, in patients who have received at least one prior therapy. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Guidelines

Calquence is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):

- **B-Cell Lymphomas**: NCCN guidelines (version 4.2023 – June 2, 2023) address mantle cell lymphoma and marginal zone lymphoma.[3,6] Calquence is recommended as one of several preferred agents as second-line and subsequent therapy for mantle cell lymphoma (category 2A); there is a footnote that states that Calquence has not been shown to be effective for Imbruvica® (ibrutinib tablets, capsules, or oral solution)-refractory mantle cell lymphoma with *BTK* C481S mutations. Patients with Imbruvica intolerance have been successfully treated with Calquence or Brukinsa® (zanubrutinib capsules) without recurrence of symptoms. For marginal zone lymphoma, NCCN guidelines recommend Calquence as a "preferred" regimen for second-line and subsequent therapy (category 2A). Calquence is also recommended as preferred aggressive induction therapy and maintenance therapy with chemotherapy (category 2B).
- **CLL/SLL**: NCCN guidelines (version 3.2023 – June 12, 2023) list Calquence as a "preferred" first-line therapy option as a single agent or in combination with Gazyva® (obinutuzumab intravenous infusion) for patients with deletion(17p)/TP53 mutation (category 2A) or without deletion(17p)/TP53 mutation (category 1).[4,6] The guidelines also list single-agent Calquence as a preferred second-line and subsequent therapy for patients with or without deletion(17p)/TP53 mutation (category 1); there is a footnote that states that Calquence has not been shown to be effective for Imbruvica-refractory CLL with *BTK* C481S mutations. Patients with Imbruvica intolerance have been successfully treated with Calquence or Brukinsa without recurrence of symptoms.
- **Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma:** NCCN guidelines (version 1.2023 – July 6, 2022) recommend single-agent Calquence as an "Other Recommended Regimen" for previously treated disease (category 2A).[5,6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Calquence. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Calquence is recommended in those who meet one of the following criteria:

FDA-Approved Indications

76. Chronic Lymphocytic Leukemia. Approve for 1 year if the patient is ≥ 18 years of age.

77. Mantle Cell Lymphoma. Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets one of the following (i or ii):
  - **i.** Patient has tried at least one systemic regimen; OR
    Note: Examples of a systemic regimen contain one or more of the following products: rituximab, dexamethasone, cytarabine, carboplatin, cisplatin, oxaliplatin, cyclophosphamide, doxorubicin, vincristine, prednisone, methotrexate, bendamustine, bortezomib, or lenalidomide,
  - **ii.** According to the prescriber, patient is not a candidate for a systemic regimen (i.e., an elderly person who is frail).

78. Small Lymphocytic Lymphoma. Approve for 1 year if the patient is ≥ 18 years of age.

Other Uses with Supportive Evidence

79. Marginal Zone Lymphoma. Approve for 1 year if the patient meets the following (A and B):
Note: Marginal zone lymphoma includes gastric mucosa-associated lymphoid tissue (MALT) lymphoma, non-gastric MALT lymphoma, nodal marginal zone lymphoma, and splenic marginal zone lymphoma.
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has tried at least one systemic regimen
  Note: Examples of a systemic regimen contain one or more of the following products: bendamustine, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, lenalidomide, or chlorambucil.

80. Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma. Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has tried at least one systemic regimen.
  Note: Examples of a systemic regimen contain one or more of the following products: Brukinsa (zanubrutinib capsules), Imbruvica (ibrutinib tablets, capsules, and oral solution), rituximab, bendamustine, cyclophosphamide, dexamethasone, bortezomib, fludarabine, or cladribine.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Calquence is not recommended in the following situations:

165. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

231. Calquence® capsules [prescribing information]. Wilmington, DE: AstraZeneca; November 2019.
232. Calquence ® tablets [prescribing information]. Wilmington, DE: AstraZeneca; August 2022.
233. The NCCN B-Cell Lymphomas Guidelines in Oncology (version 4.2023 – June 2, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 6, 2023.
234. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (version 3.2023 – June 12, 2023). © 2023 National Comprehensive Cancer Network. Available at http://www.nccn.org. Accessed on July 6, 2023.
235. The NCCN Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma Clinical Practice Guidelines in Oncology (version 1.2023 – July 6, 2022). © 2022 National Comprehensive Cancer Network. Available at http://www.nccn.org. Accessed on July 6, 2023.
236. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 6, 2023. Search term: acalabrutinib.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Capecitabine Prior Authorization
- Xeloda® (capecitabine tablets – Genentech, generic)

REVIEW DATE: 08/23/2023

OVERVIEW

Capecitabine, a nucleoside metabolic inhibitor with antineoplastic activity, is indicated for the following uses:[1]

- **Breast cancer,** treatment of advanced or metastatic disease:
  - **i.** In combination with docetaxel after disease progression on prior anthracycline-containing chemotherapy.
  - **ii.** As a single agent if an anthracycline- or taxane-containing chemotherapy is not indicated.
- **Colorectal cancer**:
  - **i.** Adjuvant treatment of patients with Stage III colon cancer as a single agent or as a component of a combination chemotherapy regimen.
  - **ii.** Perioperative treatment of adults with locally advanced rectal cancer as a component of chemoradiotherapy.
  - **iii.** Treatment of patients with unresectable or metastatic colorectal cancer as a single agent or as a component of a combination chemotherapy regimen.
- **Gastric, esophageal, or gastroesophageal junction cancer,** treatment of adults with:
  - **i.** Unresectable or metastatic disease as a component of a combination chemotherapy regimen.
  - **ii.** HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease as a component of a combination regimen.
- **Pancreatic Cancer,** adjuvant treatment of adults with pancreatic adenocarcinoma as a component of a combination chemotherapy regimen.

Guidelines

The National Comprehensive Cancer Network (NCCN) Compendium recommends use of capecitabine for the indications listed in the FDA-Approved Indications and Other Uses with Supportive Evidence sections.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of capecitabine. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of capecitabine is recommended in those who meet one of the following criteria:

FDA-Approved Indications

105. Breast Cancer. Approve for 1 year if the patient is ≥ 18 years of age.

106. Colon Cancer. Approve for 1 year if the patient is ≥ 18 years of age.

107. Esophageal and Esophagogastric Junction Cancers. Approve for 1 year if the patient is ≥ 18 years of age.

108. Gastric Cancer. Approve for 1 year if the patient is ≥ 18 years of age.

109. Pancreatic Adenocarcinoma. Approve for 1 year if the patient is ≥ 18 years of age.

Other Uses with Supportive Evidence

110. Ampullary Adenocarcinoma. Approve for 1 year if the patient is ≥ 18 years of age.

111. Anal Carcinoma. Approve for 1 year if the patient is ≥ 18 years of age.

112. Central Nervous System Cancers. Approve for 1 year if the patient is ≥ 18 years of age.

113. Gestational Trophoblastic Neoplasia. Approve for 1 year if the patient is ≥ 18 years of age.

114. Head and Neck Cancers. Approve for 1 year if the patient is ≥ 18 years of age.

115. Biliary Tract Cancer. Approve for 1 year if the patient is ≥ 18 years of age.

116. Neuroendocrine and Adrenal Tumors. Approve for 1 year if the patient is ≥ 18 years of age.

117. Occult Primary Tumors. Approve for 1 year if the patient is ≥ 18 years of age.

118. Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer. Approve for 1 year if the patient is ≥ 18 years of age.

119. Penile Cancer. Approve for 1 year if the patient is ≥ 18 years of age.

120. Rectal Cancer. Approve for 1 year if the patient is ≥ 18 years of age.

121. Small Bowel Adenocarcinoma. Approve for 1 year if the patient is ≥ 18 years of age.

122. Squamous Cell Skin Cancer. Approve for 1 year if the patient is ≥ 18 years of age.

123. Thymomas and Thymic Carcinomas. Approve for 1 year if the patient is ≥ 18 years of age.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of capecitabine is not recommended in the following situations:

340. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1089. Xeloda® tablets [prescribing information]. South San Francisco, CA: Genentech; December 2022.

1090. The NCCN Drugs & Biologics Compendium. © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 25, 2022. Search terms: capecitabine.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Caprelsa Prior Authorization Policy
- Caprelsa® (vandetanib tablets – AstraZeneca)

REVIEW DATE: 06/07/2023

OVERVIEW

Caprelsa, a kinase inhibitor, is indicated for the treatment of symptomatic or progressive **medullary thyroid cancer** in patients with unresectable locally advanced or metastatic disease.[1]

GUIDELINES

Caprelsa is discussed in guidelines from the National Comprehensive Cancer Network (NCCN). NCCN thyroid guidelines (version 2.2023 – May 18, 2023) lists surgery as the main treatment option for medullary thyroid cancer.[2,3] Caprelsa (category 1) or Cometriq® (cabozantinib capsules) [category 1] are the preferred treatments for recurrent or persistent locoregional or distant metastatic disease. For differentiated thyroid cancer subtypes, the guidelines have changed the naming of Hürthle cell neoplasm to oncocytic carcinoma. The guidelines recommend that Caprelsa can be considered if clinical trials or other systemic therapies are not available or appropriate for the treatment of progressive and/or symptomatic locally recurrent, advanced, and/or metastatic disease that is not amendable to radioactive iodine (RAI) therapy; this recommendation is for differentiated thyroid cancer (e.g. follicular, oncocytic, and papillary cancer subtypes) [all category 2A].[2,3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Caprelsa. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Caprelsa is recommended in those who meet one of the following criteria:

FDA-Approved Indication

81. Thyroid Carcinoma, Medullary. Approve for 1 year if the patient is ≥ 18 years of age.

Other Uses with Supportive Evidence

82. Thyroid Carcinoma, Differentiated. Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) Patient is ≥ 18 years of age; AND

B) Patient has differentiated thyroid carcinoma; AND

- Note: Examples of differentiated thyroid carcinoma include papillary, follicular, and oncocytic carcinoma (formerly Hürthle cell carcinoma).

C) The disease is refractory to radioactive iodine therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Caprelsa is not recommended in the following situations:

166. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

348. Caprelsa® tablets [prescribing information]. Wilmington, DE: AstraZeneca; March 2022.
349. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (version 2.2023 – May 18, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 26, 2023.
350. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 23, 2023. Search term: vandetanib.

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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Cometriq Prior Authorization Policy
- Cometriq® (cabozantinib capsules – Exelixis)

REVIEW DATE: 06/07/2023

OVERVIEW

Cometriq, a kinase inhibitor, is indicated for the treatment of patients with progressive, metastatic **medullary thyroid cancer**.[1]

Guidelines

Cometriq is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):

- **Non-Small Cell Lung Cancer:** NCCN guidelines (version 3.2023 – April 13, 2023) recommend the use of Cometriq for *RET* gene rearrangements (category 2A).[2]
- **Thyroid Carcinoma:** NCCN guidelines (version 2.2023 – May 18, 2023) list surgery as the main treatment option for medullary thyroid cancer.[3] Cometriq or Caprelsa® (vandetanib tablets) (category 1) are the preferred treatments for recurrent or persistent disease that is locoregional or metastatic. The guidelines also state that cabozantinib can be considered if patient has progression after Lenvima® (lenvatinib capsules) and/or sorafenib for the treatment of locally recurrent, advanced, and/or metastatic disease that is not amendable to radioactive iodine therapy; this recommendation is for follicular, oncocytic, and papillary cancer subtypes (all category 2A).[4] For differentiated thyroid cancer subtypes, the guidelines have changed the naming of Hürthle cell neoplasm to oncocytic carcinoma.

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95.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cometriq. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cometriq is recommended in those who meet one of the following criteria:

FDA-Approved Indication

83. Thyroid Carcinoma, Medullary. Approve for 1 year if the patient is ≥ 18 years of age.

Other Uses with Supportive Evidence

96.

84. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has *RET* gene rearrangements.

85. Thyroid Carcinoma, Differentiated. Approve for 1 year if the patient meets the following criteria (A, B, C and D):

A) Patient is ≥ 12 years of age; AND

B) Patient has differentiated thyroid carcinoma; AND

97. Note: Examples of differentiated thyroid carcinoma include papillary, follicular, and oncocytic carcinoma (formerly Hürthle cell carcinoma).

C) The disease is refractory to radioactive iodine therapy; AND

D) Patient has tried Lenvima (lenvatinib capsules) or sorafenib tablets.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cometriq is not recommended in the following situations:

98. 1. Metastatic Castration-Resistant Prostate Cancer (mCRPC). Results from the COMET-1 Phase III pivotal study with cabozantinib 60 mg tablets in men with mCRPC are published.[5] Patients included in the study had disease progression after treatment with docetaxel as well as abiraterone acetate and/or Xtandi® (enzalutamide capsules). The study failed to meet its primary endpoint of demonstrating statistically significant increase in overall survival (OS) compared with prednisone. The median OS with cabozantinib was 11.0 months vs. 9.8 months with prednisone, which was not statistically significant. Based on these results, the second Phase III study, COMET-2 has been discontinued.[6]

99.

100. 2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

351. Cometriq® capsules [prescribing information]. San Francisco, CA: Exelixis; October 2020.
352. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – April 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 23, 2023.
353. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (version 2.2023 – May 18, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 23, 2023.
354. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 23, 2023. Search term: cabozantinib.
355. Smith M, De Bono J, Sternberg C, et al. Phase III study of cabozantinib in previously treated metastatic castration-resistant prostate cancer: COMET-1. *J Clin Oncol.* 2016;34:3005-3013.
356. Exelixis. Study of cabozantinib (XL184) versus mitoxantrone plus prednisone in men with previously treated symptomatic castration-resistant prostate cancer (COMET-2). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2023 May 23]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01522443?term=NCT01522443&rank=1. NLM identifier: NCT01522443.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Copiktra Prior Authorization Policy
- Copiktra® (duvelisib capsules – Secura Bio)

REVIEW DATE: 06/28/2023

OVERVIEW

Copiktra, a phosphatidylinositol 3-kinase (PI3K) inhibitor, is indicated for the treatment of adults for relapsed or refractory **chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)** after at least two prior therapies.[1]

Guidelines

Copiktra is discussed in guidelines from the National Comprehensive Cancer Network (NCCN).

- **CLL/SLL:** NCCN guidelines (version 3.2023 – June 12, 2023) include Copiktra as subsequent therapy for relapsed or refractory disease after prior Bruton tyrosine kinase inhibitor and Venclexta (venetoclax tablets) based regimen in patients without deletion (del)[17p]/TP53 mutation as "other recommended regimens" (category 2A). Copiktra is also recommended as second-line and subsequent therapy for del(17p)/TP53 mutation as "other recommended regimens" (category 2A).[2]
- **T-Cell Lymphoma:** NCCN guidelines (version 1.2023 – January 5, 2023) recommend Copiktra as initial palliative intent therapy or second-line or and subsequent therapy for relapsed/refractory peripheral T-cell lymphoma; as second-line and subsequent therapy for relapsed/refractory disease for breast implant-associated anaplastic large cell lymphoma; and for hepatosplenic T-cell lymphoma as a single agent for refractory disease after two first-line therapy regimens.[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Copiktra. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Copiktra is recommended in those who meet one of the following:

FDA-Approved Indications

86. Chronic Lymphocytic Leukemia. Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has tried one systemic regimen.
  Note: Examples of systemic regimens include one or more of the following products: Imbruvica (ibrutinib capsules, tablets, and oral solution); Brukinsa (zanubrutinib capsules), Calquence (acalabrutinib tablets), Venclexta (venetoclax tablets); rituximab; Gazyva (obinutuzumab intravenous infusion); chlorambucil; fludarabine; cyclophosphamide; bendamustine; high-dose methylprednisolone; Campath (alemtuzumab intravenous infusion), or Arzerra (ofatumumab intravenous infusion).

87. Small Lymphocytic Lymphoma. Approve for 1 year if the patient meets the following (A and B):

A) Patient is ≥ 18 years of age; AND

B) Patient has tried one systemic regimen.

Note: Examples of systemic regimens include one or more of the following products: Imbruvica (ibrutinib capsules, tablets, and oral solution); Calquence (acalabrutinib tablets); Brukinsa (zanubrutinib capsules); Venclexta (venetoclax tablets); rituximab; Gazyva (obinutuzumab intravenous infusion); chlorambucil; fludarabine; cyclophosphamide; bendamustine; high-dose methylprednisolone; Campath (alemtuzumab intravenous infusion); or Arzerra (ofatumumab intravenous infusion).

Other Uses with Supportive Evidence

88. T-Cell Lymphoma. Approve for 1 year if the patient meets the following (A, B, and C):

A) Patient is ≥ 18 years of age; AND

B) Patient meets one of the following criteria (i or ii):

i. Patient meets both of the following criteria (a and b):

a) Patient has relapsed or refractory disease; AND

b) Patient has breast implant-associated anaplastic large cell lymphoma or hepatosplenic T-cell lymphoma; OR

ii. Patient has peripheral T-cell lymphoma

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Copiktra is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

357. Copiktra® capsules [prescribing information]. Las Vegas, NV: Secura Bio; December 2021.
358. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (version 3.2023 – June 12, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 21, 2023.
359. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 2.2022 – March 7, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 10, 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Cotellic Prior Authorization Policy
- Cotellic® (cobimetinib tablets – Genentech/Roche)

REVIEW DATE: 07/19/2023

OVERVIEW

Cotellic is a MEK inhibitor indicated for the following uses:
- **Histiocytic neoplasms,** as a single agent in adults.
- **Melanoma,** in combination with Zelboraf® (vemurafenib tablets), for the treatment of unresectable or metastatic disease with the *BRAF V600E* or *V600K* mutation in adults.[1]

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines support use in multiple cancers.[5]
- **Central Nervous System Cancers:** Guidelines (version 1.2023 – March 24, 2023) recommend a BRAF/MEK inhibitor combination (i.e., Tafinlar® [dabrafenib capsules]/Mekinist® [trametinib tablets] or Zelboraf/Cotellic) for treatment of *BRAF V600E* activation mutations in adults in the following situations: adjuvant treatment of pilocytic astrocytoma, pleomorphic xanthoastrocytoma, or ganglioglioma; recurrent or progressive low-grade glioma; oliogdenroglioma, or isocitrate dehydrogenase-2 (*IDH2*)-mutant astrocytoma; and recurrent glioblastoma.[4] BRAF/MEK combination therapy is also recommended for melanoma with brain metastases.
- **Melanoma, Cutaneous:** Guidelines (version 2.2023 – March 10, 2023) for cutaneous disease recommend BRAF/MEK inhibitor combinations among the preferred therapies for first-line and subsequent treatment of metastatic or unresectable melanoma with a *V600*-activating mutation.[2] The combinations are also recommended for adjuvant treatment (category 2B). While combination BRAF/MEK inhibition is preferred, if a combination is contraindicated, monotherapy with a BRAF inhibitor is an option, especially in patients who are not appropriate candidates for checkpoint immunotherapy.
- **Histiocytic Neoplasms:** Guidelines (version 1.2022 – May 20, 2022) recommend Cotellic (preferred) or Mekinist (other recommended regimen) for histiocytic neoplasms (if there is a MAP kinase pathway mutation, or no detectable mutation, or testing is not available) for the following types: Langerhans cell histiocytosis (including multisystem, pulmonary or central nervous system lesions), Erdheim-Chester disease, and Rosai-Dorfman disease.[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cotellic. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cotellic is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Histiocytic Neoplasm.** Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets one of the following (i, ii, or iii):
     - **i.** Patient has Langerhans cell histiocytosis and one of the following (a, b, or c):
       - **a)** Multisystem disease; OR
       - **b)** Pulmonary disease; OR
       - **c)** Central nervous system lesions; OR
     - **ii.** Patient has Erdheim-Chester disease; OR
     - **iii.** Patient has Rosai-Dorfman disease.

- **2. Melanoma.** Approve for 1 year if the patient meets the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has unresectable, advanced, or metastatic melanoma; AND
- **C)** Patient has *BRAF V600* mutation-positive disease; AND
- **D)** The medication is prescribed in combination with Zelboraf (vemurafenib tablets).

Other Uses with Supportive Evidence

3. **Central Nervous System Cancer.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** The medication is being used for one of the following (i, ii, or iii):
     - **i.** Adjuvant treatment of one of the following conditions (a, b, or c):
       - **a)** Pilocytic astrocytoma; OR
       - **b)** Pleomorphic xanthoastrocytoma; OR
       - **c)** Ganglioglioma; OR
     - **ii.** Recurrent or progressive disease for one of the following (a or d):
       - **a)** Glioma; OR
       - **b)** Isocitrate dehydrogenase-2 (IDH2)-mutant astrocytoma; OR
       - **c)** Oligodendroglioma; OR
       - **d)** Glioblastoma; OR
     - **iii.** Brain metastases due to melanoma; AND
   - **C)** Patient has *BRAF V600* mutation-positive disease; AND
   - **D)** The medication is prescribed in combination with Zelboraf (vemurafenib tablets).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cotellic is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

480. Cotellic® tablets [prescribing information]. South San Francisco, CA: Genentech/Roche; May 31, 2023.
481. The NCCN Melanoma Clinical Practice Guidelines in Oncology (version 2.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on July 14, 2023.
482. The NCCN Histiocytic Neoplasms Clinical Practice Guidelines in Oncology (version 1.2022 – May 20, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on July 14, 2023.
483. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 1.2023 – March 24, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on July 14, 2023.
484. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 10, 2023. Search terms: encorafenib.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Daurismo Prior Authorization Policy
- Daurismo™ (glasdegib tablets – Pfizer)

REVIEW DATE: 01/04/2023

OVERVIEW

Daurismo, a hedgehog pathway inhibitor, is indicated, in combination with low-dose cytarabine, for the treatment of newly diagnosed **acute myeloid leukemia** in adults who are ≥ 75 years of age or who have comorbidities that preclude use of intensive induction chemotherapy.[1]

Guidelines

Daurismo is addressed in the National Comprehensive Cancer Network (NCCN) guidelines:

- **Acute Myeloid Leukemia:** NCCN guidelines (version 2.2022 – June 14, 2022) recommend Daurismo with low-dose cytarabine for newly diagnosed patients ≥ 75 years of age, or who have significant comorbid conditions (i.e., severe cardiac disease, Eastern Cooperative Oncology Group performance status ≥ 2, baseline creatinine > 1.3 mg/dL).[2] This recommendation is for treatment induction in patients without actionable mutations who are not candidates for intensive remission induction therapy or who decline intensive therapy (category 2A).[2] It is also indicated for post-induction therapy following a response to previous lower intensity therapy with the same regimen (category 2A).[2] Daurismo is also indicated for relapsed/refractory disease as a component of repeating the initial successful induction regimen if late relapse (≥ 12 months since induction regimen), if not administered continuously and not stopped due to development of clinical resistance.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Daurismo. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Daurismo is recommended in those who meet the following criteria:

FDA-Approved Indication

124. Acute Myeloid Leukemia. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient is using the medication in combination with cytarabine.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Daurismo is not recommended in the following situations:

341. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1091. Daurismo™ tablets [prescribing information]. New York, NY: Pfizer; March 2020.

1092. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 2.2022 – June 14, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 29, 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Erivedge Prior Authorization Policy
- Erivedge® (vismodegib capsules – Genentech/Roche)

REVIEW DATE: 12/21/2022

OVERVIEW

Erivedge, an inhibitor of the hedgehog signaling pathway, is indicated for the treatment of adults with metastatic **basal cell carcinoma**, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.[1]

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines address Erivedge.

- **Basal Cell Carcinoma:** Guidelines (version 2.2022 – March 24, 2022) note that surgical approaches offer the most effective and efficient means for accomplishing a cure; radiation therapy may be chosen as the primary treatment in order to achieve optimal overall results.[2] When surgery and radiation therapy are contraindicated and for recurrent disease with nodal or distant metastases, Erivedge is among the treatment options (category 2A).
- **Central Nervous System Cancers:** Guidelines (version 2.2022 – September 29, 2022) list Erivedge as a treatment option for adults with recurrent medulloblastoma, if chemotherapy has been tried and if there is a mutation of the sonic hedgehog pathway.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Erivedge. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Erivedge is recommended in those who meet one of the following criteria:

FDA-Approved Indications

89. Basal Cell Carcinoma, Locally Advanced. Approve for 1 year if the patients meets ONE of the following conditions (A or B):

~~**1.**~~ Initial Therapy. Approve if the patient meets BOTH of the following (i and ii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient meets one of the following (a or b):
  - ~~**a)**~~ Patient has recurrent basal cell carcinoma following surgery or radiation therapy; OR
  - ~~**b)**~~ Patient meets BOTH of the following [(1) and (2)]:
    - **(1)** Patient is not a candidate for surgery; AND
    - **(2)** According to the prescriber, the patient is not a candidate for radiation therapy.

2. Patient is Currently Receiving Erivedge. Approve.

90. Basal Cell Carcinoma, Metastatic. Approve for 1 year if the patient is ≥ 18 years of age.

Note: This includes primary or recurrent nodal metastases and distant metastastatic disease.

Other Uses with Supportive Evidence

91. Central Nervous System Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
Note: This includes brain and spinal cord tumors.
A) Patient is ≥ 18 years of age; AND
B) Patient has medulloblastoma; AND
C) Patient has tried at least one chemotherapy agent; AND
Note: Examples of chemotherapy include etoposide, carboplatin, cisplatin.
D) According to the prescriber, the patient has a mutation of the sonic hedgehog pathway.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Erivedge is not recommended in the following situations:

167. Basal Cell Carcinoma (Locally Advanced or Metastatic), in a Patient with Disease Progression While on Odomzo (sonidegib capsules). Note: This does not apply to a patient already started on Erivedge. Refer to criteria for basal cell carcinoma, Locally Advanced for a Patient Currently Receiving Erivedge. There are no data to support the use of Erivedge in patients who have experienced disease progression on Odomzo. Previous use of a hedgehog inhibitor was not allowed in the pivotal study for Odomzo.[3] Patients who develop resistance to one of the hedgehog pathway inhibitors are not expected to respond to another hedgehog pathway inhibitor. There is an open-label study which evaluated patients (n = 9) with advanced basal cell carcinoma who had progressed on Erivedge that showed resistance to Odomzo, another hedgehog signaling pathway used in basal cell carcinoma.[7]

168. Metastatic Colorectal Cancer. Erivedge is not recognized in the treatment recommendations for colon cancer from the NCCN (version 3.2021 – September 10, 2021).[4] In combination with standard of care treatment for first-line disease, Erivedge did not confer incremental clinical benefit as measured by progression-free survival (PFS) compared with standard care therapy alone. A Phase II study was designed to assess whether Erivedge would prolong PFS when combined with standard of care therapy (FOLFOX [leucovorin, fluorouracil, oxaliplatin] or FOLFIRI [leucovorin, fluorouracil, irinotecan] in combination with Avastin® [bevacizumab injection]) in patients requiring first-line treatment for metastatic colorectal cancer.[3] Adults with histologically confirmed disease were randomized 1:1 to Erivedge or placebo (n = 199). There was not a significant difference is median PFS or 12-month survival with Erivedge vs. placebo.

169. Ovarian Cancer. The NCCN guidelines for Ovarian Cancer (version 3.2021 – September 9, 2021) do not address the use of Erivedge for the management of ovarian cancer.[6] The prespecified magnitude of PFS was not achieved in a Phase II, randomized, double-blind, placebo-controlled trial in adults with histologically confirmed epithelial ovarian carcinoma, primary peritoneal carcinoma, or fallopian tube carcinoma. The study was conducted to determine an estimate of clinical benefit of maintenance therapy with Erivedge in the setting of second or third complete remission as measured by PFS using radiographic assessment.[5] Eligible patients had received chemotherapy (platinum based and/or non-platinum based) for recurrent disease and had achieved complete response after their most recent chemotherapy regimen. PFS was not statistically different with Erivedge vs. placebo.

170. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

360. Erivedge® capsules [prescribing information]. South San Francisco, CA: Genentech/Roche; July 2020.
361. The NCCN Basal Cell Skin Cancer Clinical Practice Guidelines in Oncology (version 2.2022 – March 24, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 13, 2022.
362. Berlin JD, Bendell JC, Hart LL, et al. A randomized Phase II trial of vismodegib versus placebo with FOLFOX or FOLFIRI and bevacizumab in patients with previously untreated metastatic colorectal cancer. *Clin Cancer Res*. 2013;19(1):258-267.
363. NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 2.2022 – October 27, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 13, 2022.
364. Kaye SB, Fehrenbacher L, Holloway R, et al. A Phase II, randomized, placebo-controlled study of vismodegib as maintenance therapy in patients with ovarian cancer in second or third complete remission. *Clin Cancer Res*. 2012;18(23):6509-6518.
365. NCCN Ovarian Cancer Clinical Practice Guidelines in Oncology (version 5.2021 – September 16, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 13, 2022.
366. Danial C, Sarin KY, Oro AE, Chang AL. An investigator-initiated open-label trial of sonidegib in advanced basal cell carcinoma patients resistant to vismodegib. *Clin Cancer Res*. 2016;22(6):1325-1329.
367. NCCN Central Nervous System Cancer Clinical Practice Guidelines in Oncology (version 2.2022 – September 29, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 13, 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Erleada Prior Authorization Policy
- Erleada® (apalutamide tablets – Janssen)

REVIEW DATE: 04/05/2023

OVERVIEW

Erleada, an androgen receptor inhibitor, is indicated for the treatment of patients with **non-metastatic, castration-resistant prostate cancer (nmCRPC)** and **metastatic castration-sensitive prostate cancer (CSPC)**.[1] Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or the patient should have had a bilateral orchiectomy.

GUIDELINES

According to the National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (version 1.2023 – September 16, 2022)[2]:

- For nmCRPC, Erleada, Xtandi® (enzalutamide capsules or tablets), and Nubeqa® (darolutamide tablets) are all preferred category 1 recommended options, if the prostate specific antigen doubling time is ≤ 10 months.
- For mCSPC androgen deprivation therapy in combination with abiraterone + steroid, Erleada, docetaxel, and Xtandi are all preferred category 1 recommended options. Yonsa® (abiraterone acetate tablets) with methylprednisolone is a category 2B recommendation.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Erleada. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Erleada is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Prostate Cancer – Non-Metastatic, Castration-Resistant.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets ONE of the following criteria (i, ii, or iii):
     - **i.** The medication is used in combination with a gonadotropin-releasing hormone (GnRH) agonist; OR
       Note: Examples of GnRH agonists include: leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Vantas (histrelin acetate subcutaneous implant).
     - **ii.** The medication is concurrently used with Firmagon (degarelix subcutaneous injection); OR
     - **iii.** Patient has had a bilateral orchiectomy.

2. **Prostate Cancer – Metastatic, Castration-Sensitive.** Approve for 1 year if the patient meets the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets ONE of the following criteria (i, ii, or iii):
      i. The medication is used in combination with a gonadotropin-releasing hormone (GnRH) agonist; OR
      Note: Examples of GnRH agonists include: leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Vantas (histrelin acetate subcutaneous implant)
      ii. The medication is concurrently used with Firmagon (degarelix subcutaneous injection); OR
      iii. Patient has had a bilateral orchiectomy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Erleada is not recommended in the following situations:

171. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

237. Erleada® tablets [prescribing information]. Horsham, PA: Janssen; February 2023.
238. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – September 16, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed April 2, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Erlotinib Prior Authorization Policy
- Tarceva® (erlotinib tablets – Genentech, generic)

REVIEW DATE: 01/25/2023

OVERVIEW

Erlotinib, a tyrosine kinase inhibitor, is indicated for the following uses:[1]

- **Non-Small Cell Lung Cancer (NSCLC)**, treatment of patients whose tumors have epidermal growth factor receptor **(*EGFR*) exon 19 deletions** or **exon 21 (L858R) substitution mutations** as detected by an FDA-approved test, receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen. Limitations of use: The safety and efficacy of erlotinib have not been established in patients with NSCLC whose tumors have other *EGFR* mutations. Erlotinib is not recommended for use in combination with platinum-based chemotherapy.
- **Pancreatic Cancer**, in combination with gemcitabine as first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer.

Guidelines

Erlotinib has been addressed in National Comprehensive Cancer Network (NCCN) guidelines.[2-7]

- **Bone Cancer:** Guidelines (version 2.2023 – September 28, 2022) note erlotinib as a treatment option for patients with chordoma (useful in certain circumstances).[3] The efficacy of erlotinib was demonstrated in patients with advanced chordoma resistant to imatinib.
- **Non-Small Cell Lung Cancer:** Guidelines (version 1.2023 – December 22, 2022) recommend erlotinib and other *EGFR* tyrosine kinase inhibitors as first-line treatment for patients with advanced or metastatic NSCLC with *EGFR* exon 19 deletions, exon 21 (L858R) substitution mutations, L861Q, G719X, and S768I.
- **Pancreatic Adenocarcinoma:** Guidelines (version 2.2022 – December 6, 2022) recommend the combination of gemcitabine and erlotinib as first-line treatment option for patients with locally advanced or metastatic disease (other recommended regimens).[5] In addition, the combination is recommended as a subsequent therapy option for locally advanced, metastatic, or recurrent disease (other recommended regimens).
- **Kidney Cancer:** Guidelines (version 4.2023 – January 18, 2023) note erlotinib as a treatment option for patients with recurrent or advanced renal cell carcinoma of non-clear cell histology (useful in certain circumstances).[6] The combination of bevacizumab with erlotinib is a treatment option for select patients with non-clear cell and papillary cell histology, including hereditary leiomyomatosis and renal cell carcinoma (useful in certain circumstances).
- **Vulvar Cancer:** Guidelines (version 1.2023 – December 22, 2022) recommend erlotinib as a treatment option for patients with advanced, recurrent, or metastatic vulvar cancer (other recommended regimens).[7]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of erlotinib. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of erlotinib is recommended in those who meet one of the following criteria:

FDA-Approved Indications

92. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
3. Patient is ≥ 18 years of age; AND
4. Patient has advanced or metastatic disease; AND
5. Patient has sensitizing *EGFR* mutation-positive non-small cell lung cancer as detected by an approved test.
Note: Examples of sensitizing *EGFR* mutation-positive non-small cell lung cancer include the following: exon 19 deletions, exon 21 (L858R) substitution mutations, L861Q, G719X, and S768I.

93. Pancreatic Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patient has locally advanced, metastatic, or recurrent disease; AND
C) The medication is used in combination with gemcitabine.

Other Uses with Supportive Evidence

3. Bone Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patient has chordoma; AND
C) Patient has tried at least one previous therapy.

4. Renal Cell Carcinoma. Approve for 1 year if the patient meets the following criteria (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient meets one of the following criteria (i or ii):
i. Patient has recurrent or advanced renal cell carcinoma of non-clear cell histology; OR
ii. Patient meets both of the following criteria (a and b):
a) Patient has hereditary leiomyomatosis and renal cell carcinoma; AND
b) The medication is used in combination with bevacizumab.

5. Vulvar Cancer. Approve for 1 year if the patient meets the following criteria (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient has advanced, recurrent, or metastatic disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of erlotinib is not recommended in the following situations:

1. **Breast Cancer.** One Phase II, non-randomized, open-label, bi-institutional trial did not demonstrate a beneficial effect of erlotinib plus bevacizumab in patients with metastatic breast cancer with stage IV disease that was stable or had progressed after treatment with one or two chemotherapy regimens. If the patient's tumor was human epidermal growth factor receptor-2 (HER-2) positive, prior therapy with trastuzumab was required (n = 38).[8] As single-agent therapy, erlotinib had minimal activity in unselected, previously treated women with locally advanced or metastatic breast cancer in one multicenter, Phase II study (n = 69).[9] Metronomic (frequent low-dose) capecitabine tablets and cyclophosphamide plus bevacizumab and erlotinib was effective in patients with untreated advanced metastatic HER-2 negative, estrogen receptor-negative, and progesterone receptor-poor advanced breast cancer (n = 26).[10] Among 24 patients assessable for response, 4% of patients had a complete response (CR) [n = 1], 58% of patients had partial response (PR) [n = 14], 21% of patients had stable disease (SD) > 9 weeks duration (n = 5) and 4% of patients (n = 1) had early progression of disease. The overall clinical benefit (CR + PR + SD > 24 weeks) was 75% (95% confidence interval [CI]: 53, 90). Median time to progression was 43 weeks (95% CI: 21, 69). Overall survival was 108 months (95% CI: 70, 110). NCCN Breast Cancer guidelines (version 4.2022 – June 21, 2022) do not mention erlotinib.[11]

2. **Colon Cancer, Advanced**. NCCN Colon Cancer guidelines (version 2.2022 – October 27, 2022) note several drug combinations, including bevacizumab plus erlotinib, produced negative results in phase III trials involving patients with advanced colorectal cancer and these regimens are not recommended.[12] In addition, the panel recommends against the use of several medications, including erlotinib, for the treatment of patients who progressed after treatment with standard therapies.

3. **Glioblastoma Multiforme (GBM).** In one Phase II study, concurrent radiation therapy (RT) and temozolomide in combination with erlotinib in patients newly diagnosed with glioblastoma (n = 27) was not efficacious.[13] In two Phase II studies, erlotinib plus temozolomide given during and after RT produced favorable median survival, and progression free survival (PFS), as well as 12- or 14-month survival rates in patients with newly diagnosed GBM or gliosarcoma.[14,15] In patients with newly diagnosed (untreated; could have had resection) GBM or gliosarcoma who received erlotinib plus temozolomide during and after radiation, median survival was longer with erlotinib plus temozolomide vs. historical controls (19.3 months vs. 14.1 months, respectively; hazard ratio for survival 0.64; 95% confidence interval [CI]: 0.45, 0.91; P = 0.01) in one open-label, single-center, Phase II trial (n = 65).[14] The historical controls were comparable in patients from two prospective, Phase II trials (n = 128); the first trial included the use of Thalomid® (thalidomide capsules) in combination with temozolomide during and after radiotherapy; the second included the use of *cis*-retinoic acid with temozolomide during and after radiotherapy. In one open-label, Phase I/II trial, treatment with erlotinib plus temozolomide during and after RT resulted in favorable survival rate (61% of patients were alive at 1 year) and median PFS (7.2 months) in patients with newly diagnosed GBM (following resection); however, there was no significant difference in overall survival with the addition of erlotinib compared with the temozolomide/RT arm of a historical control trial (15.3 months vs. 15 months, respectively).[24] Erlotinib has failed to demonstrate benefit in recurrent glioblastomas.[16-19] In a recent study involving patients with recurrent gliobastoma, the combination regimen of sorafenib and erlotinib failed to meet the predetermined efficacy endpoint and the study was terminated.[20] NCCN Central Nervous System guidelines (version 2.2022 – September 29, 2022) do not mention erlotinib as a treatment option for patients with glioblastoma.[21]

4. **Head and Neck Cancer, Squamous Cell, Recurrent and/or Metastatic.** Two Phase II studies assessed the use of erlotinib and bevacizumab in different settings and showed promising results.[2223] One multicenter, Phase II trial assessed the addition of bevacizumab and erlotinib to chemoradiation as first-line treatment for previously untreated patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) [n = 60].[22] After a median follow-up of 32 months the estimated 3-year progression free survival (PFS) and overall survival rates were 71% and 82%, respectively. After induction therapy, 65% of patients had major responses; after completion of therapy, 95% of patients had either partial or complete radiographic responses. One multi-institutional Phase I/II study enrolled patients with recurrent or metastatic SCCHN (previously treated with ≤ 1 prior regimen for recurrent disease) to receive erlotinib and bevacizumab (n = 56).[23] The median overall survival and PFS durations were 7.1 months (95% confidence interval [CI]: 5.7, 9.0) and 4.1 months (95% CI: 2.8, 4.4), respectively. Treatment with erlotinib monotherapy produced few partial responses in unselected (*EGFR* status not known at baseline) patients with locally recurrent and/or metastatic SCCHN in one open-label, Phase II clinical trial (n = 115); 38.3% of patients achieved stable disease for a median of 16.1 weeks.[24] In one Phase II study, 204 patients with locally advanced SCCHN were randomized to receive cisplatin in combination with radiation therapy (RT) with or without erlotinib.[25] Complete response rates evaluated by central review were reported in 40% of patients (n = 42/105) on cisplatin/RT vs. 52% of patients (n = 51/99) on cisplatin/RT/erlotinib (P = 0.08). At a median follow-up of 26 months and 54 progression events, there was no difference in PFS between the two treatment arms (hazard ratio 0.0; P = 0.71). In a Phase II study, patients with recurrent SCCHN were treated with erlotinib for 12 months (n = 31). The overall survival was 61% at 1 year and 56% at 2 years.[26] Disease-free survival was 54% at 1 year and 45% at 2 years. The mean time to recurrence (n = 16) was 8.7 months. Only 8 patients completed the full 12-month course of erlotinib; the median duration of erlotinib therapy was 5 months. NCCN Head and Neck Cancer guidelines (version 1.2023 – December 20, 2022) do not mention erlotinb.[27]

5. **Hepatocellular Carcinoma, Advanced**. NCCN Hepatobiliary Cancers guidelines (version 5.2022 – January 13, 2023) note the combination regimen of sorafenib and erlotinib did not significantly improve survival compared with sorafenib monotherapy in the treatment of patients with advanced hepatocellular carcinoma (sorafenib is one of several agents recommended for first-line treatment).[28] In addition, the disease control rate was significantly lower for patients who received the combination vs. those who received sorafenib monotherapy; treatment duration was also shorter for those received sorafenib and erlotinib. .

6. **Renal Cell Carcinoma, Advanced – Clear Cell Histology.** NCCN Kidney Cancer guidelines (version 4.2023 – January 18, 2023) do not note erlotinib as a treatment option for advanced clear-cell renal cell carcinoma.[6]

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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A) PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Everolimus Products Prior Authorization Policy
- Afinitor® (everolimus tablets – Novartis, generic)
- Afinitor Disperz® (everolimus tablets for oral suspension – Novartis)

REVIEW DATE: 03/08/2023; selected revision 03/29/2023

OVERVIEW

Afinitor, a kinase inhibitor, is indicated for the following uses:[1]

- **Breast cancer**, treatment of advanced hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative disease in combination with exemestane, after failure of treatment with letrozole or anastrozole in postmenopausal women.
- **Neuroendocrine tumors (NET)**, treatment of progressive disease of pancreatic origin and progressive, well-differentiated, non-functional NET of gastrointestinal or lung origin that are unresectable, locally advanced, or metastatic in adults. Limitation of Use: Afinitor is not indicated for the treatment of patients with functional carcinoid tumors.
- **Renal cell carcinoma**, treatment of advanced disease after failure of treatment with sunitinib or sorafenib in adults.
- **Tuberous sclerosis complex (TSC)-associated renal angiomyolipoma,** treatment of adults not requiring immediate surgery.
- **TSC-associated subependymal giant cell astrocytoma (SEGA)**, treatment of patients ≥ 1 year of age who require therapeutic intervention but cannot be curatively resected.

Afinitor Disperz, a kinase inhibitor, is indicated for the following uses:[1]

- **TSC-associated subependymal giant cell astrocytoma (SEGA)**, treatment of patients ≥ 1 year of age who require therapeutic intervention but cannot be curatively resected.
- **TSC-associated partial-onset seizures**, adjunctive treatment of patients ≥ 2 years of age.

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Of note, Zortress® (everolimus tablets) is indicated in combination with other drugs for prophylaxis of organ rejection in adults undergoing kidney or liver transplant.[2] The tablet strengths and dosing are different for Zortress and Afinitor. Zortress is not targeted in this policy.

i.

Guidelines

The National Comprehensive Cancer Network (NCCN) Compendium recommends use of everolimus for the indications listed in the FDA-Approved Indications and Other Uses with Supportive Evidence sections.[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of everolimus products. All approvals are provided for the duration noted below. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: a woman is defined as an individual with the biological traits of a woman, regardless of the individual's gender identity or gender expression; men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of everolimus products is recommended in those who meet one of the following criteria:

FDA-Approved Indications

94. Breast Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, D, E, F, and G):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has recurrent or metastatic, hormone receptor positive (HR+) [i.e., estrogen receptor-positive {ER+} and/or progesterone receptor-positive {PR+}] disease; AND
- **C)** Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
- **D)** Patient has tried at least one prior endocrine therapy (e.g., anastrozole, letrozole, or tamoxifen); AND
- **E)** Patient meets ONE of the following conditions (i or ii):
  - **i.** Patient is a postmenopausal woman* or a man*; OR
  - **ii.** Patient is a pre/perimenopausal woman* and meets one of the following (a or b):
    - **a)** Patient is receiving ovarian suppression/ablation with a gonadotropin-releasing hormone (GnRH) agonist; OR

      BBBBB) Note: Examples of a GnRH agonist include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant).
    - **b)** Patient has had surgical bilateral oophorectomy or ovarian irradiation; AND
- **F)** Patient meets ONE of the following conditions (i or ii):
  - **i.** The medication will be used in combination with exemestane and the patient meets one of the following (a or b):
    - **a)** Patient is a man* and the patient is receiving a gonadotropin-releasing hormone (GnRH) analog; OR

      CCCCC) Note: Examples of a GnRH analog include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Firmagon (degarelix acetate subcutaneous injection), and Orgovyx (relugolix tablet).
    - **b)** Patient is a woman*; OR
  - **ii.** The medication will be used in combination with fulvestrant or tamoxifen; AND
- **G)** Patient has not had disease progression while on everolimus.

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*Refer to the Policy Statement.

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95. Neuroendocrine Tumors of the Pancreas, Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors). Approve for 1 year if the patient is ≥ 18 years of age.

96. Renal Cell Carcinoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has relapsed or Stage IV disease; AND
- **C)** Patient meets one of the following criteria (i or ii):
  - **i.** Patient has non-clear cell disease; OR
  - **ii.** Patient meets both of the following (a and b):
    - **a)** Patient has clear cell disease; AND
    - **b)** Patient has tried at least one prior systemic therapy.

    FFFFF) Note: Examples of prior systemic therapy include the following products: Inlyta (axitinib tablets), Lenvima (lenvatinib capsules), Cabometyx (cabozantinib tablets), Keytruda

(pembrolizumab intravenous infusion), Opdivo (nivolumab intravenous infusion), Votrient (pazopanib tablets), sunitinib.

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4. **Tuberous Sclerosis Complex-Associated Renal Angiomyolipoma.** Approve for 1 year.

5. **Tuberous Sclerosis Complex-Associated Subependymal Giant Cell Astrocytoma (SEGA).** Approve for 1 year if therapeutic intervention is required but SEGA cannot be curatively resected.

6. **Tuberous Sclerosis Complex-Associated Partial Onset Seizures.** Approve for 1 year.

Other Uses with Supportive Evidence

7. **Endometrial Carcinoma.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** The medication will be used in combination with letrozole.

8. **Gastrointestinal Stromal Tumors.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has tried each of the following (i, ii, iii, and iv):
     - **i.** One of imatinib or Ayvakit (avapritinib tablets); AND
     - **ii.** One of sunitinib or Sprycel (dasatinib tablets); AND
     - **iii.** Stivarga (regorafenib tablets); AND
     - **iv.** Qinlock (ripretinib tablets); AND
   - **C)** The medication will be used in combination with imatinib, sunitinib, or Stivarga (regorafenib tablets).

9. **Histiocytic Neoplasm.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **B)** Patient is ≥ 18 years of age; AND
   - **C)** Patient meets one of the following (i, ii, or iii):
     - **i.** Patient has Langerhans cell histiocytosis and one of the following (a, b, c, or d):
       - **a)** Bone disease; OR
       - **b)** Central nervous system lesions; OR
       - **c)** Multisystem disease; OR
       - **d)** Pulmonary disease; OR
     - **ii.** Patient has Erdheim-Chester disease; OR
     - **iii.** Patient has Rosai-Dorfman disease; AND
   - **D)** Patient has a *PIK3CA* mutation.

10. **Classic Hodgkin Lymphoma.** Approve for 1 year if the patient meets the following criteria (A and B):
    - **A)** Patient is ≥ 18 years of age; AND
    - **B)** Patient has relapsed or refractory disease.

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11. **Soft Tissue Sarcoma.** Approve for 1 year if the patient meets the following criteria (A and B):
    - **A)** Patient is ≥ 18 years of age; AND
    - **B)** Patient has one of the following conditions (i or ii):
      - **i.** Perivascular epithelioid cell tumor (PEComa); OR
      - **ii.** Recurrent angiomyolipoma/lymphangioleiomyomatosis.

12. **Thymomas and Thymic Carcinomas.** Approve for 1 year if the patient meets the following criteria (A and B):
    A) Patient is ≥ 18 years of age; AND
    B) Patient meets one of the following criteria (i or ii):
        i. Patient has tried chemotherapy; OR
        IIIII) Note: Examples are cisplatin, doxorubicin, and cyclophosphamide; cisplatin plus etoposide; carboplatin plus paclitaxel.
        ii. Patient cannot tolerate chemotherapy.

13. **Thyroid Carcinoma, Differentiated.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
    A) Patient is ≥ 18 years of age; AND
    B) Patient has differentiated thyroid carcinoma; AND
    Note: Examples of differentiated thyroid carcinoma include papillary, follicular, and Hürthle cell thyroid carcinoma.
    C) The disease is refractory to radioactive iodine therapy.
    JJJJJ)
14. **Uterine Sarcoma**. Approve for 1 year if the patient meets the following criteria (A, B, C and D):
    A) Patient is ≥ 18 years of age; AND
    B) Patient has advanced, recurrent, metastatic, or inoperable disease; AND
    C) Patient has a perivascular epithelioid cell tumor (PEComa); AND
    D) Patient has tried at least one systemic regimen.

KKKKK) Note: Examples of systemic regimen include doxorubicin, docetaxel, gemcitabine, ifosfamide, dacarbazine.

15. **Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma.** Approve for 1 year if the patient meets the following criteria (A and B):
    A) Patient is ≥ 18 years of age; AND
    B) Patient meets one of the following (i or ii):
        i. Patient has not responded to primary therapy; OR
        Note: Examples of primary therapy are bortezomib, dexamethasone, and rituximab; bendamustine and rituximab; cyclophosphamide, rituximab and dexamethasone; Imbruvica (ibrutinib capsules); and Brukinsa (zanubrutinib capsules).
        ii. Patient has progressive or relapsed disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of everolimus products is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Exkivity Prior Authorization Policy
- Exkivity™ (mobocertinib capsules – Takeda)

REVIEW DATE: 09/13/2023; selected revision 10/11/2023

OVERVIEW

Exkivity, an epidermal growth factor receptor (*EGFR*) inhibitor, is indicated for the treatment of adults with locally advanced or metastatic **non-small cell lung cancer (NSCLC)** with *EGFR* exon 20 insertion mutation, as determined by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy. Exkivity received accelerated approval for this indication in 2021; however, the drug has failed to meet its primary endpoint in its Phase III confirmatory study. Due to this, on October 2, 2023, the manufacturer announced the initiation of a voluntary withdrawal for Exkivity. The manufacturer noted that patients receiving Exkivity can continue to get access when the drug is withdrawn.

Guidelines

The National Comprehensive Cancer Network (NCCN) NSCLC guidelines (version 3.2023 – April 13, 2023) recommend Exkivity as a subsequent treatment option for patients with *EGFR* exon 20 insertion-positive metastatic NSCLC and disease progression on or after initial systemic therapy (category 2A recommendation).[2] Platinum-based chemotherapy is typically recommended as first-line for most patients with *EGFR* exon 20 insertion-positive metastatic NSCLC. Exkivity is also recommended as a treatment option for patients who progressed on Rybrevant™ (amivantamab-vmjw intravenous infusion) [category 2A recommendation]. The NCCN guidelines have not been updated to reflect Exkivity withdrawal from the market.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Exkivity. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Exkivity is recommended in those who meet the following criteria:

FDA-Approved Indication

3. **Non-Small Cell Lung Cancer.** Approve for 1 year if the patient meets the following (A, B, C, D, E, and F):
   - **A)** Patient is currently receiving Exkivity; AND
   - **B)** Patient is ≥ 18 years of age; AND
   - **C)** Patient has locally advanced or metastatic disease; AND
   - **D)** Patient has epidermal growth factor receptor (*EGFR*) exon 20 insertion-positive disease; AND
   - **E)** The mutation was determined by an approved test; AND
   - **F)** Patient has previously tried at least one platinum-based chemotherapy.

- Note: Examples of platinum-based chemotherapy include carboplatin, cisplatin, and oxaliplatin.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Exkivity is not recommended in the following situations:

13. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Farydak Prior Authorization Policy
- Farydak® (panobinostat capsules – Novartis)

REVIEW DATE: 05/31/2023

OVERVIEW

Farydak, a histone deacetylase inhibitor, was approved in combination with bortezomib injection and dexamethasone for the treatment of patients with **multiple myeloma** who have received at least two prior regimens, including bortezomib injection and an immunomodulatory drug (i.e., Thalomid® [thalidomide capsules], Revlimid® [lenalidomide capsules], Pomalyst® [pomalidomide capsules]).[1]

The FDA granted accelerated approval to Farydak in February 2015, based on progression free survival from a randomized, double-blind, placebo-controlled, multicenter, Phase III study. In December 2021, the manufacturer removed Farydak from the market because the required post-approval clinical studies were not feasible.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for multiple myeloma (version 3.2023 – December 8, 2022) note that due to market withdrawal, regimens containing Farydak were removed from the guideline.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Farydak. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Farydak is recommended in those who meet the following criteria:

FDA-Approved Indication

97. Multiple Myeloma. Approve for 1 year if the patient meets the following (A, B, C, and D):
- **6.** Patient is currently receiving Farydak; AND
- **7.** Patient has previously tried bortezomib injection; AND
- **8.** Patient has tried one immunomodulatory drug (i.e., Thalomid [thalidomide capsules], lenalidomide capsules, or Pomalyst [pomalidomide capsules]); AND
- **9.** The medication will be taken in combination with bortezomib injection and dexamethasone.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Farydak is not recommended in the following situations:

172. Pancreatic Cancer. A Phase II study evaluating Farydak + bortezomib injection in patients with pancreatic cancer who were progressing on gemcitabine-based therapy was discontinued early due to toxicity and a lack of response.[3]

173. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

368. Farydak® capsules [prescribing information]. East Hanover, NJ: Novartis; June 2016.
369. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 3.2023 – December 8, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 23, 2023.
370. Wang H, Cao Q, Dudek AZ. Phase II study of panobinostat and bortezomib in patients with pancreatic cancer progressing on gemcitabine-based therapy. *Anticancer Res.* 2012;32(3):1027-1031.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Fotivda Prior Authorization Policy
- Fotivda® (tivozanib tablets – AVEO)

REVIEW DATE: 04/19/2023

OVERVIEW

Fotivda, a kinase inhibitor, is indicated for the treatment of relapsed or refractory advanced **renal cell carcinoma (RCC)** following two or more prior systemic therapies in adults.[1]

Guidelines

In the National Comprehensive Cancer Network (NCCN) clinical practice guidelines for kidney cancer (version 4.2023 – January 18, 2023), Fotivda is given a category 2A recommendation as "useful in certain circumstances" for subsequent therapy for clear cell histology, with a footnote that states this recommendation applies to patients who have received ≥ two systemic therapies. It is also recommended under "Other recommended regimens" for subsequent therapy for clear cell histology in patients who have had prior immune-oncology therapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Fotivda. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Fotivda is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Renal Cell Carcinoma.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
1. Patient is ≥ 18 years of age; AND
1. Patient has relapsed or Stage IV disease; AND
1. Patient has tried at least two other systemic regimens.

    101. Note: Examples of systemic regimens for renal cell carcinoma include Inlyta (axitinib tablets) + Keytruda (pembrolizumab intravenous infusion), Cabometyx (cabozantinib tablets) + Opdivo (nivolumab intravenous infusion), Lenvima (lenvatinib capsules) + Keytruda, Yervoy (ipilimumab intravenous infusion) + Opdivo, sunitinib, Votrient (pazopanib tablets), and Lenvima+ everolimus.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Fotivda is not recommended in the following situations:

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

102.

103.

REFERENCES

371. Fotivda® tablets [prescribing information]. Boston, MA: AVEO; March 2021.
372. The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – January 18, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed April 18, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Fruzaqla Prior Authorization Policy
- Fruzaqla™ (fruquintinib capsules – Takeda)

REVIEW DATE: 11/15/2023; selected revision 12/13/2023

OVERVIEW

Fruzaqla; a kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3; is indicated for the treatment of **metastatic colorectal cancer** in adults who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor (VEGF) therapy, and if *RAS* wild-type and medically appropriate an anti-epidermal growth factor receptor (EGFR) therapy.

Guidelines

The National Comprehensive Cancer Network colon (version 4.2023 – November 16, 2023) and rectal (version 6.2023 – November 16, 2023) cancer treatment guidelines recommend Fruzaqla for the subsequent treatment of advanced or metastatic colon, rectal, or appendiceal cancer as a single agent.[2-4] Patients should have progressed through all available regimens except Fruzaqla, Lonsurf® (trifluridine, tipiracil tablet), and Stivarga® (regorafenib tablet).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Fruzaqla. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Fruzaqla is recommended in those who meet the following criteria:

FDA-Approved Indication

125. Colon, Rectal, or Appendiceal Cancer. Approve for 1 year if the patient meets the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has advanced or metastatic disease; AND
- **C)** Patient has previously been treated with the following (i, ii, and iii)
  - **i.** Fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; AND
    Note: Examples of fluoropyrimidine agents include 5-fluorouracil (5-FU) and capecitabine.
  - **ii.** An anti-vascular endothelial growth factor (VEGF) agent; AND
    Note: Examples of anti-VEGF agents include bevacizumab.
  - **iii.** If the tumor is *RAS* wild-type (*KRAS* wild-type and *NRAS* wild-type) [that is, the tumor or metastases are *KRAS* and *NRAS* mutation negative], the patient meets ONE of the following (a or b):
    - **a)** According to the prescriber, anti-epidermal growth factor receptor (EGFR) therapy is NOT medically appropriate; OR

b) The patient has received an anti-EGFR therapy.
Note: Examples of anti-EGFR therapy includes Erbitux (cetuximab intravenous infusion) and Vectibix (panitumumab intravenous infusion).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Fruzaqla is not recommended in the following situations:

342. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1093. Fruzaqla capsules [prescribing information]. Lexington, MA: Takeda; November 2023.
1094. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 5, 2023. Search term: fruquintinib.
1095. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – November 16, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 5, 2023.
1096. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 6.2023 – November 16, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 5, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Gavreto Prior Authorization Policy
- Gavreto® (pralsetinib capsules – Blueprint Medicines)

REVIEW DATE: 09/13/2023

OVERVIEW

Gavreto, a kinase inhibitor, is indicated for the following uses:[1]

- **Non-small cell lung cancer**, in adults with metastatic *RET* fusion-positive disease as detected by an FDA approved test.
- **Thyroid cancer**, in adults and pediatric patients ≥ 12 years of age with advanced or metastatic *RET* fusion-positive disease who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).
  This indication was approved under accelerated approval based on overall response rate and duration of response. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Guidelines

Gavreto is addressed in the National Comprehensive Cancer Network (NCCN) guidelines:

- **Non-Small Cell Lung Cancer:** Guidelines (version 3.2023 – April 13, 2023) recommend Gavreto and Retevmo® (selpercatinib capsules) as "preferred" first-line therapies for *RET* rearrangement-positive recurrent, advanced, or metastatic disease (both category 2A).[2] For patients who were started on other systemic therapy options and had disease progression, Gavreto and Retevmo are recommended as "preferred" subsequent therapies (category 2A). The NCCN compendium recommend Gavreto and Retevmo for locoregional recurrence or symptomatic local disease with *RET* rearrangement (both category 2B).[4]
- **Thyroid Carcinoma:** Guidelines (version 4.2023 – August 16, 2023) recommend the use of Gavreto and Retevmo in a variety of therapy settings.[3] The guidelines recommend Gavreto and Retevmo for differentiated thyroid carcinoma (papillary, follicular, oncocytic carcinoma) with *RET* fusion-positive tumors for unresectable locoregional recurrent or persistent disease, or distant metastatic disease that is not amenable to radioactive therapy as "useful in certain circumstances" (category 2A). For recurrent, persistent, locoregional or metastatic medullary thyroid cancer, Gavreto (category 2B) or Retevmo (category 2A) are listed as "preferred" options for *RET* mutation-positive disease. For anaplastic carcinoma, Gavreto or Retevmo can be used for *RET*-fusion positive tumors as neoadjuvant therapy for locoregional disease (category 2A). For metastatic anaplastic carcinoma, molecular testing for actionable mutations is recommended; if positive for *RET* fusion, Gavreto or Retevmo can be considered (category 2A).[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Gavreto. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Gavreto is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Differentiated Thyroid Cancer.** Approve for 1 year if the patient meets the following (A, B, C and D):

104. Note: Differentiated thyroid cancer includes papillary, follicular, and oncocytic thyroid cancer; see below for other types of thyroid cancer.

- **A)** Patient is ≥ 12 years of age; AND
- **B)** Patient has unresectable, recurrent, or metastatic disease; AND
- **C)** Patient has rearranged during transfection (*RET*) fusion-positive or *RET*-mutation-positive disease; AND
- **D)** Patient meets both of the following (i and ii):
  - **i.** The disease requires treatment with systemic therapy; AND
  - **ii.** The disease is radioactive iodine-refractory.

105.

2. **Non-Small Cell Lung Cancer.** Approve for 1 year if the patient meets the following (A, B, and C):

- **D)** Patient is ≥ 18 years of age; AND
- **E)** Patient has recurrent, advanced, or metastatic disease; AND
- **F)** Patient has rearranged during transfection (*RET*) fusion-positive disease as detected by an approved test.

Other Uses with Supportive Evidence

3. **Anaplastic Thyroid Cancer**. Approve for 1 year if the patient meets the following (A, B and C):

- **A)** Patient is ≥ 12 years of age; AND
- **B)** Patient has unresectable, recurrent, or metastatic disease; AND
- **C)** Patient has rearranged during transfection (*RET*) fusion-positive or *RET*-mutation-positive disease.

4. **Medullary Thyroid Cancer**. Approve for 1 year if the patient meets the following (A, B, C and D):

- **A)** Patient is ≥ 12 years of age; AND
- **B)** Patient has unresectable, recurrent, or metastatic disease; AND
- **C)** Patient has rearranged during transfection (*RET*) fusion-positive or *RET*-mutation-positive disease; AND
- **D)** Patient is continuing therapy with Gavreto.

106.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Gavreto is not recommended in the following situations:

343. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

107.

108.

REFERENCES

1097. Gavreto® capsules [prescribing information]. Cambridge, MA: Blueprint Medicines; April 2021.

1098. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2023– April 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed August 14, 2023.

1099. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (version 3.2023 – August 16, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on August 16, 2023.

1100. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on August 14, 2023. Search term: pralsetinib.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Gefitinib Prior Authorization Policy
- Iressa® (gefitinib tablets – AstraZeneca, generics)

REVIEW DATE: 09/06/2023

OVERVIEW

Gefitinib, a tyrosine kinase inhibitor, is indicated for the first-line treatment of patients with metastatic **non-small cell lung cancer (NSCLC)** whose tumors have epidermal growth factor receptor (*EGFR*) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.[1]

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines for NSCLC (version 3.2023 – April 13, 2023) recommend testing for sensitizing *EGFR* mutations in patients with metastatic disease.[2] Patients with sensitizing *EGFR* mutations have a significantly better response to the *EGFR* tyrosine kinase inhibitors (TKIs) [erlotinib, Gilotrif, gefitinib, Tagrisso, and Vizimpro]. The most common *EGFR* mutations are exon 19 deletions and exon 21 (L858R) substitution mutations. Other less common mutations that are also sensitive to *EGFR* TKIs include L861Q, G719X, and S768I; these mutations cumulatively account for approximately 10% of all *EGFR* mutations. NCCN recommends the *EGFR* TKIs as first-line treatment for patients with advanced or metastatic NSCLC with *EGFR* exon 19 deletions, exon 21 (L858R) substitution mutations, L861Q, G719X, and S768I.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of gefitinib. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of gefitinib is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Non-Small Cell Lung Cancer.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   - **98.** Patient is ≥ 18 years of age; AND
   - **99.** Patient has advanced or metastatic disease; AND
   - **100.** Patient has sensitizing *EGFR* mutation-positive disease; AND
     Note: Examples of sensitizing *EGFR* mutation-positive non-small cell lung cancer include the following: exon 19 deletions, exon 21 (L858R) substitution mutations, L861Q, G719X, and S768I.
   - **101.** The mutation was detected by an approved test.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of gefitinib is not recommended in the following situations:

174. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

485. Iressa® tablets [prescribing information]. Wilmington, DE: AstraZeneca; May 2021.

486. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – April 13, 2023). © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 28, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Gilotrif Prior Authorization Policy
- Gilotrif® (afatinib tablets – Boehringer Ingelheim)

REVIEW DATE: 11/29/2023

OVERVIEW

Gilotrif, a tyrosine kinase inhibitor (TKI), is indicated for the following uses:[1]

- **Non-small cell lung cancer (NSCLC)**, first-line treatment of patients with metastatic disease whose tumors have non-resistant epidermal growth factor receptor (*EGFR*) mutations as detected by an FDA-approved test.
  Limitations of use: The safety and efficacy of Gilotrif have not been established in patients whose tumors have resistant *EGFR* mutations.
- **NSCLC, squamous cell,** for the treatment of patients with metastatic disease progressing after platinum-based chemotherapy.

Guidelines

Gilotrif has been addressed in National Comprehensive Cancer Network (NCCN) guidelines.[2-4]

- **Head and Neck Cancer:** Guidelines (version 1.2024 – October 9, 2023) recommend Gilotrif as a single agent for the treatment of recurrent, unresectable, or metastatic non-nasopharyngeal cancers (lip, oral cavity, oropharynx, hypopharynx, glottis, larynx, supraglottic, larynx, ethmoid sinus, maxillary sinus, occult primary) in patients with disease progression or after platinum-based therapy (category 2B).[3]
- **Non-Small Cell Lung Cancer (NSCLC)**: Guidelines (version 5.2023 – November 8, 2023) recommend testing for sensitizing *EGFR* mutations in patients with metastatic disease.[4] Patients with sensitizing EGFR mutations have a significantly better response to the *EGFR* tyrosine kinase inhibitors (TKIs) [erlotinib, Gilotrif, Iressa®, Tagrisso®, and Vizimpro]. The most common *EGFR* mutations are exon 19 deletions and exon 21 (L858R) substitution mutations. Other less common mutations that are also sensitive to *EGFR* TKIs include L861Q, G719X, and S768I; these mutations cumulatively account for approximately 10% of all EGFR mutations. NCCN recommends the *EGFR* TKIs as first-line treatment for patients with advanced or metastatic NSCLC with *EGFR* exon 19 deletions, exon 21 (L858R) substitution mutations, L861Q, G719X, and S768I. NCCN does not recommend Gilotrif for use as second-line treatment for patients with squamous cell NSCLC (without *EGFR* mutations); NCCN notes Gilotrif to be less efficacious and safe compared with other available options.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Gilotrif. All approvals are provided for duration as noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Gilotrif is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Non-Small Cell Lung Cancer – Epidermal Growth Factor Receptor (*EGFR*) Mutation-Positive.** Approve for 1 year if the patient meets the following (A, B, and C):
   10. Patient is ≥ 18 years of age; AND
   ~~**11.**~~ Patient has advanced or metastatic disease; AND
   ~~**12.**~~ Patient has sensitizing *EGFR* mutation-positive non-small cell lung cancer as detected by an approved test.
   Note: Examples of sensitizing *EGFR* mutation-positive non-small cell lung cancer include the following: exon 19 deletions, exon 21 (L858R) substitution mutations, L861Q, G719X, and S768I.

2. **Non-Small Cell Lung Cancer – Squamous Cell Carcinoma.** Approve for 1 year if the patient meets the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has metastatic squamous cell carcinoma; AND
   C) Patient has disease progression after treatment with platinum-based chemotherapy.

Other Uses with Supportive Evidence

3. **Head and Neck Cancer.** Approve for 1 year if the patient meets the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has non-nasopharyngeal head and neck cancer; AND
   Note: Examples of non-nasopharyngeal head and neck cancer are lip, oral cavity, oropharynx, hypopharynx, glottis, larynx, supraglottic larynx, ethmoid sinus, maxillary sinus, occult primary.
   C) Patient has disease progression on or after platinum-based chemotherapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Gilotrif is not recommended in the following situations:

175. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

487. Gilotrif™ tablets [prescribing information]. Ridgefield, CT: Boehringer Ingelheim; April 2022.
488. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 27, 2023. Search terms: afatinib.
489. The NCCN Head and Neck Cancer Clinical Practice Guidelines in Oncology (version 1.2024 – October 9, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 27, 2023.
490. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 5.2023 – November 8, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 27, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Ibrance Prior Authorization Policy
- Ibrance® (palbociclib capsules and tablets – Pfizer)

REVIEW DATE: 02/22/2023

OVERVIEW

Ibrance, a cyclin-dependent kinase (CDK) 4/6 inhibitor, is indicated for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative **advanced or metastatic breast cancer** in adults, in combination with:[1]

- An aromatase inhibitor (AI) as initial endocrine-based therapy.
- Fulvestrant in patients with disease progression following endocrine therapy.

176.

Guidelines

Ibrance is discussed in in guidelines from National Comprehensive Cancer Network (NCCN):

- **Breast Cancer:** NCCN guidelines (version 2.2023 – February 7, 2023) recommend Ibrance + AI or fulvestrant (category 2A) as a first-line "Preferred Regimen".[2,3] CDK4/6 inhibitor + fulvestrant is recommended for second- and subsequent-line therapy as a "Preferred Regimen", if CDK4/6 inhibitor was not previously used (category 1). However, the guidelines state in a footnote that if there is disease progression on Ibrance, there are limited phase II data to support the use of Kisqali® (ribociclib tablets) in the second-line setting.[2,3] The guidelines state that in Phase III randomized controlled trials, fulvestrant in combination with a CDK4/6 inhibitor has shown overall survival benefit in the second-line setting. The compendium recommends that men with breast cancer be treated similarly to postmenopausal women, except that the use of an AI is ineffective without concomitant suppression of testicular steroidogenesis.[3]
- **Liposarcoma:** NCCN guidelines on soft tissue sarcoma (version 2.2022 – May 17, 2022) recommend Ibrance as single-agent therapy for the treatment of unresectable well-differentiated/dedifferentiated liposarcoma for retroperitoneal sarcomas as "Useful In Certain Circumstances" (category 2A).[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ibrance. All approvals are provided for the duration noted below. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: a woman is defined as an individual with the biological traits of a woman, regardless of the individual's gender identity or gender expression; men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ibrance is recommended in those who meet one of the following criteria:

FDA-Approved Indications

102. Breast Cancer in a Woman*. Approve for 1 year if the patient meets the following criteria (A, B, C, D, E, and F):

13. Patient is ≥ 18 years of age; AND

14. Patient has recurrent or metastatic disease; AND

15. Patient has hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND

16. Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND

17. Patient meets ONE of the following criteria (i or ii):

i. Patient is postmenopausal; OR

ii. Patient is pre/perimenopausal and meets one of the following (a or b):

a) Patient is receiving ovarian suppression/ablation with a gonadotropin-releasing hormone (GnRH) agonist; OR

177. Note: Examples of a GnRH agonist include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous injection).

b) Patient has had surgical bilateral oophorectomy or ovarian irradiation; AND

18. Patient meets ONE of the following criteria (i or ii):

i. Ibrance will be used in combination with anastrozole, exemestane, or letrozole; OR

ii. Ibrance will be used in combination with fulvestrant.

***** Refer to the Policy Statement.

2. Breast Cancer in a Man*. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):

A) Patient is ≥ 18 years of age; AND

B) Patient has recurrent or metastatic disease; AND

C) Patient has hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND

D) Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND

E) Patient meets ONE of the following criteria (i or ii):

i. Patient meets BOTH of the following criteria (a and b):

a) Patient is receiving a gonadotropin-releasing hormone (GnRH) analog; AND
Note: Examples of a GnRH analog include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Firmagon (degarelix acetate subcutaneous injection), Orgovyx (relugolix tablet).

b) Ibrance will be used in combination with anastrozole, exemestane, or letrozole; OR

ii. Ibrance will be used in combination with fulvestrant.

***** Refer to the Policy Statement.

Other Uses with Supportive Evidence

3. Liposarcoma. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient is ≥ 18 years of age; AND

B) Patient has well-differentiated/dedifferentiated liposarcoma.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ibrance is not recommended in the following situations:

178. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

491. Ibrance® capsules and tablets [prescribing information]. New York, NY: Pfizer Labs; December 2022.
492. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – February 7, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 10, 2023.
493. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 10, 2023. Search terms: palbociclib.
494. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 2.2022 – May 17, 2022) © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 10, 2023.

GnRH – Gonadotropin-releasing hormone.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Iclusig Prior Authorization Policy
- Iclusig® (ponatinib tablets – ARIAD/Takeda)

REVIEW DATE: 05/31/2023

OVERVIEW

Iclusig, a tyrosine kinase inhibitor (TKI), is indicated for the following uses in adults:[1]
- Philadelphia chromosome-positive (Ph+) **acute lymphoblastic leukemia** (ALL) for whom no other TKIs are indicated.
- Ph+ **ALL, T315I-positive**.
- **Chronic myeloid leukemia** (CML), chronic phase, with resistance or intolerance to at least two prior TKIs.
- **CML**, accelerated phase or blast phase.
- **CML, T315I-positive** (chronic phase, accelerated phase, or blast phase).

A limitation of use is that Iclusig is not indicated and is not recommended for the treatment of patients with newly diagnosed chronic phase CML.

Guidelines

Iclusig is addressed in guidelines from National Comprehensive Cancer Network (NCCN):[2-4]
- **Acute Lymphoblastic Leukemia (ALL):** NCCN guidelines (version 1.2022 – April 4, 2022) [adults] recommend Iclusig as a treatment option for patients with the T315I mutation and/or for patients for whom no other TKI is indicated (category 2A).[2] Iclusig has also shown promising activity when included in various regimens.
- **CML:** NCCN guidelines (version 1.2023 – March 24, 2023) recommend Iclusig as an option for patients with a T315I mutation and/or chronic phase CML with resistance or intolerance to at least two prior TKIs or for patients with accelerated-phase CML or blast-phase CML for whom no other TKI is indicated (category 2A).
- **Gastrointestinal Stromal Tumor (GIST)**: NCCN guidelines (version 1.2023 – March 13, 2023) recommend Iclusig as "useful in certain circumstances" after failure on approved therapies (category 2A); the guidelines state the Iclusig has demonstrated activity in advanced GIST, particularly in patients with *KIT* exon 11 mutant disease.[4] Imatinib is a preferred regimen for first-line therapy (category 1) for sensitive mutations (excluding platelet-derived growth factor receptor alpha [*PDGFRA]* exon 18 mutations that are insensitive to imatinib including D842V mutation). Ayvakit® (avapritinib tablets) is also a preferred regimen (category 2A) for GIST with *PDGFRA* exon 18 mutations that are insensitive to imatinib, including the *PDGFRA* D842V mutation. Second-line therapies include sunitinib as "preferred" (category 1) and Sprycel as "other recommended regimen" (category 2A). Stivarga® (regorafenib tablets) is a "preferred" third-line therapy (category 1). Qinlock™ (ripretinib tablets) is a "preferred" fourth-line therapy (category 1).
- **Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions:** NCCN guidelines (version 1.2023 – May 19, 2023) recommend Iclusig for *ABL1* and *FGFR1* rearrangements in chronic phase or blast phase as "other recommended regimens" (category 2A).[5] It is also recommended as treatment in combination with ALL- or acute myeloid leukemia-type induction chemotherapy followed by allogeneic hematopoietic stem cell transplantation (HSCT)

[if eligible] for lymphoid, myeloid or mixed lineage neoplasms with eosinophilia and *ABL1* and *FGFR1* rearrangements in blast phase (category 2A).

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Iclusig. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Iclusig is recommended in those who meet one of the following criteria:

FDA-Approved Indications

103. Acute Lymphoblastic Leukemia. Approve for 1 year if the patient meets the following criteria (A, B, and C):
C) Patient is ≥ 18 years of age; AND
D) Patient has Philadelphia chromosome-positive acute lymphoblastic leukemia; AND
E) Patient meets one of the following criteria (i or ii):
i. The acute lymphoblastic leukemia is T315I-positive; OR
ii. Patient has tried at least two other tyrosine kinase inhibitors that are used for Philadelphia chromosome-positive acute lymphoblastic leukemia.
Note: Examples include imatinib and Sprycel (dasatinib tablets).

104. Chronic Myeloid Leukemia (CML). Approve for 1 year if the patient meets the following criteria (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patient has Philadelphia chromosome-positive chronic myeloid leukemia; AND
C) Patient meets one of the following criteria (i, ii or iii):
i. The chronic myeloid leukemia is T315I-positive, OR
ii. Patient has tried at least two other tyrosine kinase inhibitors indicated for use in Philadelphia chromosome-positive chronic myeloid leukemia; OR
Note: Examples include imatinib, Sprycel (dasatinib tablets), and Tasigna (nilotinib capsules).
iii. Patient meets the following criteria (a and b):
a) Patient has accelerated-phase CML or blast-phase CML; AND
b) No other tyrosine kinase inhibitor is indicated.

Other Uses with Supportive Evidence

3. Gastrointestinal Stromal Tumor. Approve for 1 year if the patient meets the following criteria (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient has tried each of the following (i, ii, iii, and iv):
i. One of imatinib or Ayvakit (avapritinib tablets); AND
ii. One of sunitinib or Sprycel (dasatinib tablets); AND
iii. Stivarga (regorafenib tablets); AND
iv. Qinlock (ripretinib tablets).

4. **Myeloid/Lymphoid Neoplasms with Eosinophilia.** Approve for 1 year if the patient meets the following criteria (A and B):

C) Patient is ≥ 18 years of age; AND

D) Patient meets one of the following criteria (i or ii):

i. The tumor has an *ABL1* rearrangement; OR

ii. The tumor has an *FGFR1* rearrangement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Iclusig is not recommended in the following situations:

179. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Idhifa Prior Authorization Policy
- Idhifa® (enasidenib tablets – Celgene/Servier/Bristol-Myers Squibb)

REVIEW DATE: 03/08/2023

OVERVIEW
Idhifa, an isocitrate dehydrogenase-2 *(IDH2*) inhibitor, is indicated for the treatment of relapsed or refractory **acute myeloid leukemia** in adults with an *IDH2* mutation as detected by an FDA-approved test.[1]

Guidelines
The National Comprehensive Cancer Network (NCCN) guidelines on acute myeloid leukemia (version 1.2023 – March 3, 2023) note Idhifa as an alternative for *IDH2* mutated AML in a variety of clinical scenarios, such as treatment induction, follow-up after induction therapy, consolidation therapy, or relapsed or refractory disease (category 2A).

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Idhifa. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Idhifa is recommended in those who meet the following criteria:

FDA-Approved Indication

105. Acute Myeloid Leukemia. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has isocitrate dehydrogenase-2 (*IDH2*) mutation-positive disease as detected by an approved test.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Idhifa is not recommended in the following situations:

180. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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240. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 1.2023 – March 3, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 6, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Imatinib Prior Authorization Policy
- Gleevec® (imatinib tablets– Novartis, generic)

REVIEW DATE: 05/31/2023

OVERVIEW

Imatinib, a tyrosine kinase inhibitor (TKI), is indicated for the following uses:[1,2]

- **Acute lymphoblastic leukemia (ALL)**, Philadelphia chromosome positive (Ph+), in adults with relapsed or refractory disease.
- **ALL**, newly diagnosed and Ph+, in combination with chemotherapy in pediatric patients.
- **Aggressive systemic mastocytosis**, without the D816V c-Kit mutation or with unknown c-Kit mutational status, in adults.
- **Chronic myeloid leukemia (CML)**, newly diagnosed and Ph+, chronic phase in adult and pediatric patients.
- **CML**, Ph+, in blast phase, accelerated phase, or in chronic phase in patients after failure of interferon alfa therapy.
- **Dermatofibrosarcoma protuberans** in adults with unresectable, current, and/or metastatic disease.
- **Gastrointestinal stromal tumors (GIST)**, in patients with KIT (CD117) positive unresectable and/or metastatic malignant disease.
- **GIST**, Kit (CD117) positive, as adjuvant treatment of adults following resection.
- **Hypereosinophilic syndrome and/or chronic eosinophilic leukemia**, in adults who have the *FIP1L1-PDGFR* alpha fusion kinase (mutation analysis or fluorescence in situ hybridization demonstration of CICH2 allele deletion) and for patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who are *FIP1l1-PDGFR* alpha fusion kinase negative or unknown.
- **Myelodysplastic/myeloproliferative diseases**, associated with *PDGFR* gene rearrangements in adults.

Guidelines

Imatinib is addressed in guidelines from National Comprehensive Cancer Network (NCCN):

- **ALL:** NCCN guidelines for adults and adolescents (version 1.2022 – April 4, 2022) recommend imatinib for Ph+ disease in many different clinical circumstances (e.g., induction, consolidation therapy, maintenance, or relapsed or refractory disease) [category 2A].[3] NCCN guidelines for pediatric ALL (version 2.2023 – March 10, 2023) feature imatinib prominently (category 2A) in a variety of clinical scenarios.[4]
- **Bone Cancer:** NCCN guidelines (version 3.2023 – April 4, 2023) recommend imatinib either as monotherapy or as "other recommended regimens" or in combination with cisplatin or Rapamune® (sirolimus tablets) for chordoma as "useful in certain circumstances" (both category 2A).[5]
- **CML:** NCCN guidelines (version 2.2023 – April 13, 2023) state that for patients with chronic phase CML with a low-risk score, the primary treatment recommendations includes a first-generation TKI (imatinib) or a second-generation TKI (Bosulif® [bosutinib tablets], Sprycel® [dasatinib tablets], or Tasigna® [nilotinib capsules] {all category 1}).[6] For patients with chronic phase CML with an intermediate- or high-risk score, a second-generation TKI is preferred (Bosulif, Sprycel, or Tasigna [all category 1]); imatinib is an alternative (category 2A); imatinib is also recommended for other clinical scenarios (category 2A).

- **Dermatofibrosarcoma Protuberans:** NCCN guidelines (version 1.2023 – December 8, 2022) recommend to consider neoadjuvant imatinib for unresectable/borderline disease (category 2A) and for recurrent or metastatic disease in cases where the disease is unresectable, or unacceptable functional or adverse cosmetic outcomes may occur with resection (category 2A).[7]
- **GIST:** NCCN guidelines (version 1.2023 – March 13, 2023) recommend imatinib as a "preferred regimen" for first-line therapy (category 1) in various scenarios (e.g., for sensitive mutations or for *PDGFRA* exon 18 mutations [excluding the D842V mutation) and is recommended in other clinical scenarios (e.g., neoadjuvant and adjuvant therapy)[category 2A].[8]
- **Graft-Versus-Host Disease (GVHD):** NCCN guidelines for hematopoietic cell transplantation (version 1.2023 – March 31, 2023) address GVHD.[9] Imatinib is cited as one of many therapies recommended for steroid-refractory, chronic GVHD (category 2A).
- **Kaposi Sarcoma:** NCCN guidelines (version 1.2023 – December 20, 2022) recommend imatinib for subsequent systemic therapy for relapsed/refractory therapy as "useful in certain circumstances".[10] First-line systemic therapy options are liposomal doxorubicin as "preferred regimen" and paclitaxel.
- **Melanoma: Cutaneous:** NCCN guidelines (version 2.2023 – March 10, 2023) recommend imatinib as second-line or subsequent therapy for metastatic or unresectable disease for tumors with activating mutations of *KIT* as "useful in certain circumstances" (category 2A).[11]
- **Myelodysplastic Syndromes:** NCCN guidelines (version 1.2023 – September 12, 2022) note that data have demonstrated that patients with chronic myelomonocytic leukemia who have *PDGFRβ* gene rearrangement at 5q32 may respond well to imatinib.[12]
- **Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions:** NCCN guidelines (version 1.2023 – May 19, 2023) recommend imatinib for patients with *ABL1* rearrangements in the chronic phase or blast phase (category 2A).[13] Imatinib is also recommended for certain situations where the tumor has an FIP1L1-PDGFRA or PDGFRB rearrangement (category 2A). Imatinib is also recommended for treatment in combination with ALL- or acute myeloid leukemia-type induction chemotherapy followed by allogeneic hematopoietic stem cell transplantation (if eligible) for lymphoid, myeloid or mixed lineage neoplasms with eosinophilia and ABL1 rearrangement in blast phase (category 2A).
- **Soft Tissue Sarcomas:** NCCN guidelines (version 2.2023 – April 25, 2023) recommend imatinib for desmoid tumors (aggressive fibromatosis) as a "preferred regimen" (category 2A). For dermatofibrosarcoma protuberans with fibrosarcomatous transformation, imatinib is recommended as a "preferred regimen" (category 2A). For pigmented villonodular synovitis/tenosynovial giant cell tumor, imatinib is recommended as "useful in certain circumstances" (category 2A).[14]
- **Systemic Mastocytosis:** NCCN guidelines (version 1.2023 – May 24, 2023,) recommend imatinib (for *KIT* D816V mutation negative or unknown; well differentiated systemic mastocytosis; eosinophilia is present with *FIP1L1-PDGFRA* fusion gene) for aggressive systemic mastocytosis as "useful in certain circumstances" (category 2A).[15]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of imatinib tablets. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of imatinib is recommended in those who meet one of the following criteria:

FDA-Approved Indications

~~5.~~ **Acute Lymphoblastic Leukemia.** Approve for 1 year if the patient has Philadelphia chromosome-positive acute lymphoblastic leukemia.

~~6.~~ **Aggressive Systemic Mastocytosis.** Approve for 1 year if the patient is ≥ 18 years of age.

~~7.~~ **Chronic Myeloid Leukemia.** Approve for 1 year if the patient has Philadelphia chromosome-positive chronic myeloid leukemia.

8. **Dermatofibrosarcoma Protuberans.** Approve for 1 year if the patient is ≥ 18 years of age.

~~9.~~ **Gastrointestinal Stromal Tumors.** Approve for 1 year.

~~10.~~ **Hypereosinophilic Syndrome and/or Chronic Eosinophilic Leukemia.** Approve for 1 year if the patient is ≥ 18 years of age.

11. **Myelodysplastic/Myeloproliferative Disease.** Approve for 1 year if the patient meets the following criteria (A and B):
    A) Patient is ≥ 18 years of age; AND
    B) The condition is associated with platelet-derived growth factor receptor (*PDGFR*) gene rearrangements.

Other Uses with Supportive Evidence

~~12.~~ **Chordoma.** Approve for 1 year.

13. **Desmoid Tumors (Aggressive Fibromatosis.** Approve for 1 year

~~14.~~ **Graft-Versus-Host Disease, Chronic.** Approve for 1 year if the patient has tried at least one conventional systemic treatment for graft-versus-host disease.
    Note: Examples include corticosteroids (methylprednisolone, prednisone); cyclosporine; tacrolimus; mycophenolate mofetil; Imbruvica (ibrutinib capsules, tablets, and oral suspension); low-dose methotrexate; sirolimus; Rezurock (belumosudil tablets); and Jakafi (ruxolitinib tablets).

15. **Kaposi Sarcoma.** Approve for 1 year if the patient meets the following criteria (A, B and C):
    A) Patient is ≥ 18 years of age; AND
    B) Patient has tried at least one medication; AND
    Note: Examples include liposomal doxorubicin, paclitaxel, Pomalyst (pomalidomide capsules), lenalidomide, etoposide, and Thalomid (thalidomide capsules).
    C) Patient has relapsed or refractory disease.

~~16.~~ **Melanoma, Cutaneous.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
    A) Patient is ≥ 18 years of age; AND
    B) Patient has metastatic or unresectable disease; AND
    C) Patient has an activating *KIT* mutation; AND
    D) Patient has tried at least one systemic regimen.
    Note: Examples of a systemic regimen include: Opdivo (nivolumab intravenous infusion) + Yervoy (ipilimumab intravenous infusion), Opdivo + Opdualag (nivolumab/relatlimab-rmbw

intravenous infusion), Keytruda (pembrolizumab intravenous infusion), Opdivo, Tafinlar (dabrafenib capsules) + Mekinist (trametinib tablets), Zelboraf (vemurafenib tablets) + Cotellic (cobimetinib tablets), Braftovi (encorafenib capsules) + Mektovi (binimetinib tablets).

17. Myeloid/Lymphoid Neoplasms with Eosinophilia. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets one of the following criteria (i or ii):
  - **i.** The tumor has an *ABL1* rearrangement; OR
  - **ii.** The tumor has an *FIP1L1-PDGFRA* or *PDGFRB* rearrangement.

~~**18.**~~ **Pigmented Villonodular Synovitis/Tenosynovial Giant Cell Tumor.** Approve for 1 year if the patient meets one of the following criteria (A or B):
- **A)** Patient has tried Turalio (pexidartinib capsules); OR
- **B)** Patient cannot take Turalio, according to the prescriber.
  Note: Examples of reasons for not being able to take Turalio include patients with elevated liver enzymes or concomitant use of medications that are associated with hepatotoxicity.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of imatinib is not recommend in the following situations:

181. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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384. The NCCN Dermatofibrosarcoma Protuberans Clinical Practice Guidelines in Oncology (version 1.2023 – December 8, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 12, 2023.
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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Imbruvica Prior Authorization Policy
- Imbruvica® (ibrutinib tablets, capsules, and oral suspension – Pharmacyclics/Janssen)

REVIEW DATE: 07/12/2023

OVERVIEW

Imbruvica, a Bruton's tyrosine kinase inhibitor, is indicated for the following uses:[1]
- **Chronic lymphocytic leukemia (CLL)** or **small lymphocytic lymphoma (SLL),** in adults.
- **CLL** or **SLL,** with 17p deletion, in adults.
- **Graft-versus-host disease, chronic**, after failure of one or more lines of systemic therapy in adults and pediatric patients ≥ 1 year old.
- **Waldenström macroglobulinemia,** in adults.

Guidelines

Imbruvica is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):
- **B-Cell Lymphomas:** NCCN guidelines (version 4.2023 – June 2, 2023) address mantle cell lymphoma, marginal zone lymphoma, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, non-gastric MALT lymphoma, diffuse large B-cell lymphomas, Acquired Immune Deficiency Syndrome (AIDS)-related B-Cell lymphomas, and post-transplant lymphoproliferative disorders.[2] For mantle cell lymphoma, Imbruvica + rituximab can be used as pretreatment in order to limit the number of cycles of aggressive induction therapy with RHyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen (category 2A); Imbruvica ± rituximab is recommended as second-line and subsequent therapy as "other recommended regimen" and Imbruvica + venetoclax as "useful in certain circumstances" (both category 2A).[2] Imbruvica is recommended a preferred aggressive induction therapy as a component of TRIANGLE regimen: alternating RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) + covalent Bruton tyrosine kinase inhibitor (Imbruvica)/RDHAP (rituximab, dexamethasone, and cytarabine) + carboplatin regimen (category 2A). Imbruvica can also be used in combination with rituximab as maintenance therapy (category 2A). For marginal zone lymphoma, Imbruvica is recommended as second-line and subsequent therapy as "other recommended regimens" (category 2A). For mantle cell and marginal zone lymphoma, there is a footnote that states head-to-head clinical trials in other B-cell malignancies have demonstrated a more favorable toxicity profile for Calquence and Brukinsa compared to Imbruvica without compromising efficacy. The NCCN compendium recommends Imbruvica as a second-line and subsequent therapy for diffuse large B-cell lymphomas, HIV-related B-Cell lymphomas, post-transplant lymphoproliferative disorders, and high-grade B-cell lymphoma (category 2A).[3]
- **Central Nervous System (CNS) Cancers**: NCCN guidelines (version 1.2023 – March 24, 2023) recommend Imbruvica as one of the options for patients with relapsed or refractory disease for primary CNS lymphoma as "other recommended regimens" (category 2A).[4] The guidelines also recommend Imbruvica for induction therapy as a single agent as "useful in certain circumstances" if the patient is unsuitable for or intolerant to high-dose methotrexate (category 2A).[4] Imbruvica is used with high-dose methotrexate and rituximab in some clinical scenarios.[4] Imbruvica is also recommended as treatment for brain metastases in lymphoma (category 2A).
- **CLL/SLL:** NCCN guidelines (version 3.2023 – June 12, 2023) recommend Imbruvica as a treatment option in various scenarios (e.g., first-line therapy for patients with or without 17p deletion/TP53 mutation and as second-line and third therapy [category 1 recommendations for

many scenarios]) as "other recommended regimens".[5] Imbruvica plays a vital role in the management of CLL/SLL and many trials describe its efficacy.[5]

- **Hairy Cell Leukemia**: NCCN guidelines (version 1.2023 – August 30, 2022) recommend Imbruvica as one of the options for treatment of progressive disease after therapy for relapsed or refractory disease (category 2A).[6]
- **Graft-Versus-Host Disease:** NCCN guidelines for hematopoietic stem cell transplantation (version 1.2023 – March 31, 2023) recommend Imbruvica as a systemic agent for steroid-refractory chronic graft-versus-host disease after failure of one or more lines of systemic therapy (category 2A).[7] The guidelines note that Imbruvica should be used with caution in patients with of heart arrhythmias or heightened risk of bleeding.
- **Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphomas:** NCCN guidelines (version 1.2023 – July 6, 2022) recommend Imbruvica, with or without rituximab, as a primary therapy option as one of several "preferred" regimens (category 1).[8] For previously treated patients, Imbruvica, with or without rituximab, is also cited as a "preferred" regimen (category 1). Imbruvica is also a "preferred" regimen for symptomatic management of Bing Neel Syndrome (category 2A).[8]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Imbruvica. All approvals are provided for the duration noted below.

Automation: When available, the ICD-9/ICD-10 codes for patients ≥ 18 years of age with chronic lymphocytic leukemia (ICD-9: 204.1* [lymphoid leukemia chronic] and ICD-10: C91.1* [chronic lymphocytic leukemia of B-cell type]), small lymphocytic lymphoma (ICD-10: C83.0* [small cell B-cell lymphoma]) and Waldenström macroglobulinemia (ICD-9: 273.3* [macroglobulinemia] and ICD-10: C88.0* [Waldenström macroglobulinemia]) will be used as part of automation to allow approval of the requested medication.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Imbruvica is recommended in those who meet one of the following criteria:

FDA-Approved Indications

106. Chronic Lymphocytic Leukemia. Approve for 1 year if the patient is ≥ 18 years of age.

107. Graft-Versus-Host Disease, Chronic: Approve for 1 year if the patient meets the following (A and B):

A) Patient is ≥ 1 year of age; AND

B) Patient has tried at least one conventional systemic treatment for graft-versus-host disease.
Note: Examples of conventional systemic treatments include: corticosteroids (methylprednisolone, prednisone), imatinib, low-dose methotrexate, sirolimus, mycophenolate mofetil, and Jakafi (ruxolitinib tablets).

108. Small Lymphocytic Lymphoma. Approve for 1 year if the patient is ≥ 18 years of age.

A)

109. Waldenström Macroglobulinemia. Approve for 1 year if the patient is ≥ 18 years of age.
Note: This includes lymphoplasmacytic lymphoma and Bing-Neel syndrome.

Other Uses with Supportive Evidence

110. B-Cell Lymphoma. Approve for 1 year if the patient meets the following (A and B):
Note: Examples of B-cell lymphomas include: diffuse large B-cell lymphomas, Human immunodeficiency virus (HIV)-related B-cell lymphomas, post-transplant lymphoproliferative disorders, and high-grade B-cell lymphoma.
A) Patient is ≥ 18 years of age; AND
B) Patient has tried at least one systemic regimen.
Note: Examples of a systemic regimen include one or more of the following products: cisplatin, cytarabine, rituximab, oxaliplatin, gemcitabine, ifosfamide, carboplatin, etoposide, or rituximab.

111. Central Nervous System Lymphoma (Primary). Approve for 1 year if the patient meets the following (A and B):
A) Patient ≥ 18 years of age; AND
B) Patient meets one of the following criteria (i or ii):
i. According to the prescriber, the patient is not a candidate for or is intolerant to high-dose methotrexate; OR
ii. Patient has tried at least one therapy.
Note: Examples of therapies include methotrexate, rituximab, vincristine, procarbazine, cytarabine, thiotepa, carmustine, intrathecal methotrexate, cytarabine, or rituximab.

112. Hairy Cell Leukemia. Approve for 1 year if the patient meets the following (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient has tried at least two systemic regimens.
Note: Examples of a systemic regimen include one or more of the following products: cladribine, Nipent (pentostatin injection), rituximab, or Pegasys (peginterferon alfa-2a subcutaneous injection).

113. Mantle Cell Lymphoma. Approve for 1 year if the patient meets the following (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient meets one of the following (i, iii, or iii):
i. Patient is continuing therapy with Imbruvica and meets one of the following criteria (a or b):
a) Patient has tried at least one systemic regimen; OR
Note: Examples of a systemic regimen include one or more of the following products: bendamustine, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, cytarabine, carboplatin, cisplatin, oxaliplatin, or lenalidomide.
b) According to the prescriber, patient is not a candidate for a systemic regimen (i.e., an elderly person who is frail); OR
ii. Imbruvica is used in combination with rituximab prior to induction therapy; OR
Note: Examples of induction therapy include: rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone.
iii. Imbruvica is used as induction or maintenance therapy in combination with chemotherapy.

114. Marginal Zone Lymphoma. Approve for 1 year if the patient meets the following (A, B and C):
B) Note: Marginal zone lymphoma includes gastric mucosa-associated lymphoid tissue (MALT) lymphoma, non-gastric MALT lymphoma, nodal marginal zone lymphoma, and splenic marginal zone lymphoma.
C) Patient is ≥ 18 years of age; AND
D) Patient is continuing therapy with Imbruvica; AND
E) Patient has tried at least one systemic regimen.
Note: Examples of a systemic regimen include one or more of the following products: bendamustine, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, or lenalidomide.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Imbruvica is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Inlyta Prior Authorization Policy
- Inlyta® (axitinib tablets – Pfizer)

REVIEW DATE: 06/07/2023

OVERVIEW

Inlyta, a kinase inhibitor, is indicated for **advanced renal cell carcinoma**, in combination with Bavencio® (avelumab intravenous infusion) as first-line treatment; in combination with Keytruda® (pembrolizumab intravenous infusion) as first-line treatment; and as a single agent after failure of one prior systemic therapy.[1]

Guidelines

Inlyta is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):

- **Kidney Cancer:** NCCN guidelines (version 4.2023 – January 18, 2023) for relapse or stage IV disease with clear cell histology recommend the following: Inlyta + Keytruda as a "preferred regimen" (category 1), Inlyta + Bavencio as one of the "other recommended regimens" (category 2A), and single agent Inlyta as "useful in certain circumstances" (category 2B). For subsequent therapy for clear cell histology, Inlyta monotherapy and Inlyta + Keytruda are category 2A options; Inlyta + Bavencio is a category 3 option. Single agent Inlyta is one of the systemic therapy options listed under "useful under certain circumstances" for relapse or Stage IV renal cell carcinoma with non-clear cell histology (category 2A).[2]
- **Soft Tissue Sarcoma:** NCCN guidelines (version 2.2023 – April 25, 2023) recommend Inlyta in combination with Keytruda as a preferred regimen for alveolar soft part sarcoma (category 2A).[3]
- **Thyroid Carcinoma:** For differentiated thyroid cancer subtypes, the NCCN guidelines (version 2.2023 – May 18, 2023) have changed the naming of Hürthle cell neoplasm to oncocytic carcinoma.[4] The guidelines recommend Inlyta as one of the kinase inhibitors to be considered if clinical trials or other systemic therapies are not available or appropriate for the treatment of progressive and/or symptomatic iodine refractory thyroid cancer. This recommendation is for all differentiated thyroid cancer subtypes (follicular, oncocytic, and papillary cancer) [all category 2A].

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Inlyta. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Inlyta is recommended in those who meet one of the following criteria:

FDA-Approved Indication

115. Renal Cell Cancer. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has relapsed or advanced disease.

Other Uses with Supportive Evidence

116. Soft Tissue Sarcoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has alveolar soft part sarcoma; AND
- **C)** The medication will be used in combination with Keytruda (pembrolizumab intravenous infusion).
-

117. Thyroid Carcinoma, Differentiated. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has differentiated thyroid carcinoma; AND
- Note: Examples of differentiated thyroid carcinoma include papillary, follicular, and oncocytic carcinoma (formerly Hürthle cell carcinoma).
- **C)** The disease is refractory to radioactive iodine therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Inlyta is not recommended in the following situations:

182. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.
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REFERENCES

401. Inlyta® tablets [prescribing information]. New York, NY: Pfizer; September 2022.
402. The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – January 18, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 2, 2023.
403. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 2, 2023.
404. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (version 2.2023 – May 18, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 2, 2023.

~~**109.**~~

~~**110.**~~

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Inqovi Prior Authorization Policy
- Inqovi® (decitabine and cedazuridine tablets – Taiho Oncology/Otsuka)

REVIEW DATE: 08/30/2023

OVERVIEW

Inqovi, a combination of decitabine (a nucleoside metabolic inhibitor) and cedazuridine (a cytidine deaminase inhibitor), is indicated for the treatment of **myelodysplastic syndrome** (MDS), including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System (IPSS) groups in adults.[1]

Decitabine is available as a parenteral product (Dacogen® [decitabine intravenous infusion]; generic) and possesses the same FDA-approved indication as Inqovi.[2] The oral bioavailability of decitabine is limited due to rapid degradation by cytidine deaminase in the gut and liver.[1] As a cytidine deaminase inhibitor, cedazuridine increases decitabine concentrations to therapeutic levels. Oral decitabine has systemic exposure equivalent to the intravenous form with similar clinical response rates in the population in which Inqovi is approved.[1,2] The recommended dose of Inqovi is one tablet taken orally once daily on Days 1 through 5 of each 28-day cycle for a minimum of four cycles until disease progression or unacceptable toxicity. A complete or partial response may take longer than four cycles. In the two pivotal trials, the median treatment duration was up to 8 months. Do not substitute Inqovi for the intravenous decitabine product within a cycle.

Guidelines

Inqovi is discussed in guidelines from the National Comprehensive Cancer Network (NCCN) for MDS. These guidelines (version 1.2023 – September 12, 2022) state that Inqovi can be considered as a substitute for intravenous decitabine. The guidelines recommend intravenous decitabine in patients with IPSS intermediate-1 and above, CMML, and MDS/myeloproliferative neoplasm overlap neoplasms.[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Inqovi. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Inqovi is recommended in those who meet one of the following criteria:

FDA-Approved Indications

126. Chronic Myelomonocytic Leukemia. Approve for 1 year if the patient is ≥ 18 years of age.

127. Myelodysplastic Syndrome. Approve for 1 year if the patient is ≥ 18 years of age.
Note: Examples of myelodysplastic syndromes include: refractory anemia, refractory anemia with ringed sideroblasts, and refractory anemia with excess blasts.

Other Uses with Supportive Evidence

128. Myelodysplastic Syndrome/Myeloproliferative Neoplasm Overlap Neoplasms. Approve for 1 year if the patient is ≥ 18 years of age.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Inqovi is not recommended in the following situations:

344. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

495. Inqovi® tablets [prescribing information]. Princeton, NJ and Japan: Taiho Oncology and Otsuka; March 2022.
496. Dacogen® intravenous infusion [prescribing information]. Rockville, MD and Dublin, CA: Otsuka and Astex; June 2020.
497. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 1.2023 – September 12, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed August 24, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Inrebic Prior Authorization Policy
- Inrebic® (fedratinib capsules – Celgene)

REVIEW DATE: 10/11/2023

OVERVIEW

Inrebic, a Janus Associated Kinase 2 (*JAK2*)-selective kinase inhibitor, is indicated for the treatment of **intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis** in adults.[1]

Guidelines

Inrebic is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):

- **Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions**: Guidelines (version 2.2023 – July 14, 2023) recommend Inrebic for treatment of myeloid/lymphoid neoplasms with eosinophilia and *JAK2* rearrangement in chronic phase or blast phase (category 2A).[2] The guidelines also recommend Inrebic for treatment in combination with acute lymphocytic leukemia or acute myeloid leukemia-type induction chemotherapy followed by allogeneic hematopoietic stem cell transplantation (if eligible) for lymphoid, myeloid, or mixed lineage neoplasms with eosinophilia and *JAK2* rearrangement in blast phase (category 2A).[2]
- **Myeloproliferative Neoplasms**: Guidelines (version 2.2023 – August 29, 2023) recommend Inrebic for higher-risk patients with a platelet count $\geq 50 \times 10^9$/L (category 1) who are not transplant candidates and for patients who did not have a response or lost response to Jakafi® (ruxolitinib tablets) or Vonjo® (pacritinib capsule) [category 2A].[3,4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Inrebic. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Inrebic is recommended in those who meet one of the following criteria:

FDA-Approved Indication

- **Myelofibrosis.** Approve for 1 year if the patient meets the following (A and B):

Note: Examples of myelofibrosis include primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis.

  - Patient is ≥ 18 years of age; AND
  - Patient has intermediate-2 or high-risk disease.

Other Uses with Supportive Evidence

- **Myeloid or Lymphoid Neoplasms.** Approve for 1 year if the patient meets the following (A, B, and C):

E) Patient is ≥ 18 years of age; AND
F) Patient has eosinophilia; AND
G) The tumor has a Janus Associated Kinase 2 (*JAK2)* rearrangement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Inrebic is not recommended in the following situations:

345. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1101. Inrebic® capsules [prescribing information]. Summit, NJ: Celgene; May 2023.
1102. The NCCN Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusion Clinical Practice Guidelines in Oncology (version 2.2023 – July 14, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed October 6, 2023.
1103. The NCCN Myeloproliferative Neoplasms Clinical Practice Guidelines in Oncology (version 2.2023 – August 29, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 6, 2023.
1104. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed October 6, 2023. Search term: fedratinib.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Iwilfin Prior Authorization Policy
- Iwilfin™ (eflornithine tablets – US WorldMeds)

REVIEW DATE: 01/03/2024

OVERVIEW

Iwilfin, an ornithine decarboxylase inhibitor, is indicated to reduce the risk of relapse in high-risk neuroblastoma in adults and pediatric patients with who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-glycolipid disialoganglioside (GD2) immunotherapy.[1]

Guidelines

Iwilfin is not addressed in the National Comprehensive Cancer Network (NCCN) guidelines. NCCN does not have neuroblastoma clinical practice guidelines. The treatment of high risk neuroblastoma is divided into three phases: induction, consolidation, and post-consolidation.[2] In the induction phase, treatment includes multiagent chemotherapy, peripheral blood stem cell harvest, and surgical resection of the primary site. In the consolidation phase, treatment includes high-dose chemotherapy, autologous stem cell transplantation (ASCT), and radiation or radiotherapy. In the post-consolidation phase, treatment includes anti-GD2 immunotherapy (Unituxin® [dinutuximab intravenous infusion]) in combination with isotretinoin, interleukin-2, and granulocyte-macrophage colony-stimulating factor. For patients who have recurrent or refractory neuroblastoma, treatment options include clinical trial, chemotherapy combined with immunotherapy (e.g. temozolomide, irinotecan, and Unituxin), iodine-131 meta-iodobenzylguanidine alone or in combination with other therapy, or followed by stem cell rescue, novel therapies, chemotherapy, or immunotherapy (e.g. Danyelza® [naxitamab-gqgk intravenous infusion]).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Iwilfin. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Iwilfin is recommended in those who meet the following criteria:

FDA-Approved Indication

129. Neuroblastoma Approve for 1 year if the patient meets the following (A, B and C):
- **A)** Patient has high-risk disease; AND
- **B)** The medication is being used to reduce the risk of relapse; AND
- **C)** Patient has had at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy.

Note: Examples of anti-glycolipid disialoganglioside (GD2) immunotherapy includes Unituxin® (dinutuximab intravenous infusion).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Iwilfin is not recommended in the following situations:

346. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1105. Iwilfin™ tablets [prescribing information]. Louisville, KY: USWM; December 2023.

1106. National Cancer Institute: PDQ® Neuroblastoma treatment. National Cancer Institute. Date last modified: August 22, 2023. Available at http://www.cancer.gov/cancertopics/pdq/treatment/neuroblastoma/HealthProfessional. Accessed on December 22, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Jakafi Prior Authorization Policy
- Jakafi® (ruxolitinib tablets – Incyte)

REVIEW DATE: 03/22/2023

OVERVIEW

Jakafi, an inhibitor of Janus Associated Kinases (*JAKs*) *JAK1* and *JAK2*, is indicated for the following uses:[1]

- **Graft versus host disease**, acute treatment of steroid-refractory disease, in patients ≥ 12 years of age.
- **Graft versus host disease**, chronic treatment, after failure of one or two lines of systemic therapy in patients ≥ 12 years of age.
- **Myelofibrosis**, intermediate or high risk, including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis in adults.
- **Polycythemia vera**, in adults who have had an inadequate response to or are intolerant of hydroxyurea.

Guidelines

Jakafi is discussed in guidelines by the National Comprehensive Cancer Network (NCCN):[2]

- **Graft versus host disease:** NCCN has guidelines regarding hematopoietic cell transplantation that discuss graft versus host disease (version 3.2022 – January 24, 2023) that include Jakafi.[3] Jakafi is recommended among patients with steroid-refractory acute graft versus host disease, or chronic graft versus host disease, after failure of one or two lines of systemic therapy (both category 1).[3]
- **Myelodysplastic syndromes:** NCCN guidelines (version 1.2023 – September 12, 2022) recommend Jakafi for patients with chronic myelomonocytic leukemia-2, with hypomethylating agents (HMA) and/or allogenic hematopoietic stem cell transplant (category 2A).[4] Jakafi ± HMA is also recommended for myelodysplastic syndrome/myeloproliferative neoplasm with neutrophilia (atypical chronic myeloid leukemia); there is a footnote, which states that rare patients with *CSF3R* or *JAK2* mutations may respond to Jakafi due to their JAK-STAT pathway activation (category 2A).
- **Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase fusion genes**: NCCN guidelines (version 2.2022 – October 18, 2022) recommend Jakafi for treatment of myeloid/lymphoid neoplasms with eosinophilia and *JAK2* rearrangement in chronic or blast phase (category 2A).[5] The guidelines also recommend Jakafi for treatment in combination with acute lymphocytic leukemia or acute myeloid leukemia type induction chemotherapy followed by allogeneic hematopoietic stem cell transplantation (if eligible) for lymphoid, myeloid, or mixed lineage neoplasms with eosinophilia and *JAK2* rearrangement in blast phase (category 2A).
- **Myeloproliferative neoplasms:** NCCN guidelines (version 3.2022 – August 11, 2022) recommend Jakafi among patients with lower- or higher-risk myelofibrosis (category 2A; category 1 for the initial treatment of higher-risk myelofibrosis).[6] It is also a recommended "Preferred" therapy for patients with symptomatic low-risk (category 2A) or high-risk (category 1) polycythemia vera after other agents (e.g., hydroxyurea or Pegasys® [peginterferon alfa-2a subcutaneous injection]). The guidelines also recommend Jakafi for treatment of essential thrombocythemia for inadequate response or loss of response to hydroxyurea, Pegasys therapy, or anagrelide as "Useful in Certain Circumstances" (category 2A).
- **Pediatric acute lymphoblastic leukemia:** NCCN guidelines (version 1.2023 – November 9, 2022) recommend Jakafi in a variety of regimens for pediatric patients and young adults with acute

lymphoblastic leukemia (category 2A).[7] The utility of Jakafi is described primarily in patients in which the mutation/pathway is *JAK*-related.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Jakafi. All approvals are provided for the duration noted below.

Automation: The ICD-9/ICD-10 codes for myelofibrosis (ICD-9: 289.83 and ICD-10: D75.81) will be used as part of automation to allow approval of the requested medication.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Jakafi is recommended in those who meet one of the following criteria:

FDA-Approved Indications

118. Graft versus Host Disease, Acute. Approve for 1 year if the patient meets the following criteria (A and B):
A) Patient is ≥ 12 years of age; AND
B) Patient has tried one systemic corticosteroid.

119. Graft versus Host Disease, Chronic. Approve for 1 year if the patient meets the following criteria (A and B):
A) Patient is ≥ 12 years of age; AND
B) Patient has tried one conventional systemic treatment for graft versus host disease.
Note: Examples include systemic corticosteroids (methylprednisolone, prednisone), cyclosporine, tacrolimus, mycophenolate mofetil, Imbruvica (ibrutinib capsules and tablets), and imatinib.

120. Myelofibrosis (MF), including Primary MF, Post-Polycythemia Vera MF, and Post-Essential Thrombocythemia MF. Approve for 1 year if the patient is ≥ 18 years of age.

121. Polycythemia Vera. Approve for 1 year if the patient meets the following criteria (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient has tried hydroxyurea or Pegasys (peginterferon alfa-2a subcutaneous injection).

Other Uses with Supportive Evidence

122. Acute Lymphoblastic Leukemia. Approve for 1 year if the patient meets the following criteria (A and B)
A) Patient is < 21 years of age; AND
B) The mutation/pathway is Janus Associated Kinase (*JAK*)-related.

123. Atypical Chronic Myeloid Leukemia. Approve for 1 year if the patient meets one of following criteria (A or B):
A) Patient has a *CSF3R* mutation; OR
B) Patient has a Janus Associated Kinase 2 (*JAK2*) mutation.

124. Chronic Myelomonocytic Leukemia-2. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient is ≥ 18 years of age; AND
B) Patient is also receiving a hypomethylating agent.
Note: Examples of hypomethylating agents include azacitidine and decitabine.

125. Essential Thrombocythemia. Approve for 1 year if the patient meets the following criteria (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient has tried hydroxyurea, Pegasys (peginterferon alfa-2a subcutaneous injection), or anagrelide.

126. Myeloid or Lymphoid Neoplasms. Approve for 1 year if the patient meets the following criteria (A, B, and C):
H) Patient is ≥ 18 years of age; AND
I) Patient has eosinophilia; AND
J) The tumor has a Janus Associated Kinase 2 (*JAK2)* rearrangement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Jakafi is not recommended in the following situations:

183. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

405. Jakafi® tablets [prescribing information]. Wilmington, DE: Incyte; September 2021.
406. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 7, 2023. Search term: ruxolitinib.
407. The NCCN Hematopoietic Cell Transplantation Clinical Practice Guidelines in Oncology (version 3.2022 – January 24, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 7, 2023.
408. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 1.2023 – September 12, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 7, 2023.
409. The NCCN Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes Clinical Practice Guidelines in Oncology (version 2.2022 – October 18, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 7, 2023.
410. The NCCN Myeloproliferative Neoplasms Clinical Practice Guidelines in Oncology (version 3.2022 – August 11, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 7, 2023.
411. The NCCN Pediatric Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 1.2023 – November 9, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 7, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Jaypirca Prior Authorization Policy
- Jaypirca® (pirtobrutinib tablets – Eli Lilly)

REVIEW DATE: 12/13/2023

OVERVIEW

Jaypirca, a Bruton tyrosine kinase (BTK) inhibitor, is indicated for the treatment of:

- Chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL), in adults who have received at least two prior lines of therapy, including a BTK inhibitor and B-cell lymphoma-2 (BCL-2) inhibitor.
- Mantle cell lymphoma, relapsed or refractory in adults after at least two lines of systemic therapy, including a BTK inhibitor.[1]

  Both indications are approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Guidelines

Jaypirca is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):

- **B-Cell Lymphoma**: NCCN guidelines (version 6.2023 – October 10, 2023) discuss mantle cell lymphoma.[2,4] Brukinsa® (zanubrutinib capsules) and Calquence® (acalabrutinib tablets) [both covalent BTK inhibitors] are cited as "Preferred Regimens" for second-line and subsequent therapy (both category 2A). Imbruvica® (ibrutinib capsules, tablets and oral suspension) [also a covalent BTK inhibitor], given with or without rituximab, is cited as an "Other Recommended Regimen" for second-line and subsequent therapy (category 2A). Jaypirca, a non-covalent BTK inhibitor, is recommended as a third-line and subsequent therapy (category 2A). Jaypirca inhibits both wild type and C481S mutant BTK and has been shown to be effective in patients with intolerance or disease that is refractory to prior covalent BTK inhibitors without recurrence of prior symptoms; the agent may be used for disease progression or intolerance to covalent BTK inhibitor therapy. It is noted that head-to-head clinical trials in other B-cell malignancies have demonstrated a more favorable toxicity profile for Brukinsa and Calquence compared with Imbruvica without compromising efficacy. Imbruvica + Venclexta (venetoclax tablets) is cited as "Useful in Certain Circumstances" for second-line and subsequent therapy (category 2A).
- **Chronic Lymphocytic Leukemia (CLL)**: NCCN guidelines (version 1.2024 – November 3, 2023) recommend Jaypirca for CLL or SLL with or without del(17p)/TP53 mutation as second-line or third-line therapy as "Useful in Certain Circumstances" for resistance or intolerance to prior covalent BTK inhibitor (category 2A). Jaypirca is also listed as "Other Recommended Regimens" for relapsed or refractory disease after prior BTK inhibitor and venetoclax-based regimens (if not previously used) [category 2A]. Jaypirca is also recommended as additional therapy for histologic (Richter's) transformation to diffuse large B-cell lymphoma (clonally related or unknown clonal status) as a single agent in patients with del(17p)/TP53 mutation or who are chemotherapy refractory or unable to receive chemoimmunotherapy (category 2A).[3,4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Jaypirca. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Jaypirca is recommended in those who meet one of the following criteria:

FDA-Approved Indication

130. Chronic Lymphocytic Leukemia. Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets one of the following (i or ii):
  - **i.** Patient has resistance or intolerance to Imbruvica (ibrutinib tablets, capsules, or oral solution), Calquence (acalabrutinib tablets), or Brukinsa (zanubrutinib capsules); OR
  - **ii.** Patient meets both of the following (a and b):
    - **a)** Patient has relapsed or refractory disease; AND
    - **b)** Patient meets both of the following [(1) and (2)]:
      - **(1)** Patient has tried a Bruton tyrosine kinase (BTK) inhibitor; AND
        Note: Examples of Bruton tyrosine kinase inhibitor include: Imbruvica (ibrutinib tablets, capsules, or oral solution), Calquence (acalabrutinib tablets), or Brukinsa (zanubrutinib capsules).
      - **(2)** Patient has tried Venclexta (venetoclax tablet).

131. Mantle Cell Lymphoma. Approve for 1 year if the patient meets the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets one of the following (i or ii):
  - **i.** Patient has tried at least one systemic regimen; OR
    Note: Examples of a systemic regimen contain one or more of the following products: rituximab, dexamethasone, cytarabine, carboplatin, cisplastin, oxaliplatin, cyclophosphamide, doxorubicin, vincristine, prednisone, methotrexate, bendamustine, Velcade (bortezomib intravenous or subcutaneous injection), and lenalidomide.
  - **ii.** According to the prescriber, patient is not a candidate for a systemic regimen (i.e., an elderly patient who is frail); AND
- **C)** Patient has tried one Bruton tyrosine kinase inhibitor (BTK) for mantle cell lymphoma.
  Note: Examples of BTK inhibitors indicated for mantle cell lymphoma include Brukinsa (zanubrutinib capsules), Calquence (acalabrutinib tablets), and Imbruvica (ibrutinib capsules, tablets, and oral suspension).

132. Small Lymphocytic Lymphoma. Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets one of the following (i or ii):
  - **i.** Patient has resistance or intolerance to Imbruvica (ibrutinib tablets, capsules, or oral solution), Calquence (acalabrutinib tablets), or Brukinsa (zanubrutinib capsules); OR
  - **ii.** Patient meets both of the following (a and b):
    - **a)** Patient has relapsed or refractory disease; AND
    - **b)** Patient meets both of the following [(1) and (2)]:
      - **(1)** Patient has tried a Bruton tyrosine kinase (BTK) inhibitor; AND

Note: Examples of Bruton tyrosine kinase inhibitor include: Imbruvica (ibrutinib tablets, capsules, or oral solution), Calquence (acalabrutinib tablets), or Brukinsa (zanubrutinib capsules).

(2) Patient has tried Venclexta (venetoclax tablet).

Other Uses with Supportive Evidence

133. Richter's Transformation to Diffuse Large B-Cell Lymphoma. Approve for 1 year if the patient meets the following (A and B):

A) Patient is ≥ 18 years of age; AND

B) Patient meets one of the following (i or ii):

i. Patient has tried at least one chemotherapy regimen; OR
Note: Examples of a chemotherapy regimen include: EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab); HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine + rituximab, oxaliplatin; OFAR (oxaliplatin, fludarabine, cytarabine, rituximab); RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone); and venetoclax + RCHOP

ii. Patient is not a candidate for a chemotherapy regimen.
Note: Examples of a chemotherapy regimen include: EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab); HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine + rituximab, oxaliplatin; OFAR (oxaliplatin, fludarabine, cytarabine, rituximab); RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone); and venetoclax + RCHOP

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Jaypirca is not recommended in the following situations:

347. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1107. Jaypirca™ tablets [prescribing information]. Indianapolis, IN: Eli Lilly; December 2023.

1108. The NCCN B-Cell Lymphomas Guidelines in Oncology (version 6.2023 – October 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 11, 2023.

1109. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (version 1.2024 – November 3, 2023). © 2023 National Comprehensive Cancer Network. Available at http://www.nccn.org. Accessed on December 11, 2023.

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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Kisqali and Kisqali Femara Co-Pack Prior Authorization Policy
- Kisqali® (ribociclib tablets – Novartis)
- Kisqali® Femara® Co-Pack (ribociclib tablets; letrozole tablets – Novartis)

REVIEW DATE: 02/22/2023

OVERVIEW

Kisqali, a cyclin-dependent kinase (CDK) 4/6 inhibitor, is indicated for the treatment of adults with hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative **advanced or metastatic breast cancer** in the following settings:[1-3]
- In combination with an aromatase inhibitor (AI) as initial endocrine-based therapy;
- Kisqali (not Co-Pack) in combination with fulvestrant as initial endocrine based therapy or following disease progression on endocrine therapy in postmenopausal women or in men;
- Kisqali Femara Co-Pack has the same indication with AI, letrozole, included.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on breast cancer (version 2.2023– February 7, 2023) recommends Kisqali + AI or fulvestrant as a first-line "Preferred Regimen" for HR+ and HER2-negative recurrent unresectable (local or regional) or Stage IV disease in postmenopausal women or premenopausal patient receiving ovarian ablation or suppression (category 1).[3,4] The guidelines state in a footnote that in phase III randomized controlled trials, Kisqali + endocrine therapy has shown overall survival benefit in the first-line setting. CDK4/6 inhibitor + fulvestrant is recommended as a "Preferred Regimen" for second- and subsequent-line therapy, if CDK4/6 inhibitor was not previously used (category 1). However, the guidelines also state in a footnote that if there is disease progression on Ibrance® (palbociclib tablets or capsules), there are limited data to support the use of Kisqali in the second-line setting.[3,4] The guidelines state that in phase III randomized controlled trials, fulvestrant in combination with a CDK4/6 inhibitor has shown overall survival benefit in the second-line setting. For men with breast cancer, the compendium recommends they be treated similarly to postmenopausal women, except that the use of an AI is ineffective without concomitant suppression of testicular steroidogenesis.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Kisqali and Kisqali Femara Co-Pack. All approvals are provided for the duration noted below. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: a woman is defined as an individual with the biological traits of a woman, regardless of the individual's gender identity or gender expression; men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Kisqali is recommended in those who meet one of the following criteria:

FDA-Approved Indications

127. Breast Cancer in Women*. Approve for 1 year if the patient meets the following criteria (A, B, C, D, E, and F):
19. Patient is ≥ 18 years of age; AND
20. Patient has recurrent or metastatic disease; AND
21. Patient has hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND
22. Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
23. Patient meets ONE of the following criteria (i or ii):
i. Patient is postmenopausal; OR
ii. Patient is pre/perimenopausal and meets one of the following (a or b):
a) Patient is receiving ovarian suppression/ablation with a gonadotropin-releasing hormone (GnRH) agonist; OR
184. Note: Examples of a GnRH agonist include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant).
b) Patient has had surgical bilateral oophorectomy or ovarian irradiation; AND
24. Patient meets ONE of the following criteria (i or ii):
185. i. Kisqali will be used in combination with anastrozole, exemestane, or letrozole; OR
186. ii. Kisqali will be used in combination with fulvestrant.

***** Refer to the Policy Statement.

2. Breast Cancer in Men*. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
F) Patient is ≥ 18 years of age; AND
G) Patient has recurrent or metastatic disease; AND
H) Patient has hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND
I) Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
J) Patient meets ONE of the following criteria (i or ii):
i. Patient meets BOTH of the following criteria (a and b):
a) Patient is receiving a gonadotropin-releasing hormone (GnRH) analog; AND
Note: Examples of GnRH analog include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Firmagon (degarelix acetate subcutaneous injection), Orgovyx (relugolix tablet).
b) Kisqali will be used in combination with anastrozole, exemestane, or letrozole; OR
ii. Kisqali will be used in combination with fulvestrant.

***** Refer to the Policy Statement.

II. Coverage of Kisqali Femara Co-Pack is recommended in those who meet one of the following criteria:
187.
FDA-Approved Indications

1. **Breast Cancer in Women***. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
   128. Patient is ≥ 18 years of age; AND
   129. Patient has recurrent or metastatic disease; AND
   130. Patient has hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND
   131. Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
   132. Patient meets ONE of the following criteria (i or ii):
   i. Patient is postmenopausal OR
   ii. Patient is pre/perimenopausal and meets one of the following (a or b):
   a) Patient is receiving ovarian suppression/ablation with a gonadotropin-releasing hormone (GnRH) agonist; OR
   188. Note: Examples of a GnRH agonist include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant).
   b) Patient has had surgical bilateral oophorectomy or ovarian irradiation.

   ***** Refer to the Policy Statement.

2 **Breast Cancer in Men*.** Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has recurrent or metastatic disease; AND
   C) Patient has hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND
   D) Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
   E) Patient is receiving a gonadotropin-releasing hormone (GnRH) analog.
   189. Note: Examples of a GnRH analog include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Firmagon (degarelix acetate subcutaneous injection), Orgovyx (relugolix tablet).

   ***** Refer to the Policy Statement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Kisqali or Kisqali Femara Co-Pack is not recommended in the following situations:

190. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

498. Kisqali® tablets [prescribing information]. East Hanover, NJ: Novartis; October 2022.
499. Kisqali® Femara® Co-Pack tablets [prescribing information]. East Hanover, NJ: Novartis; October 2022.
500. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – February 7, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 10, 2023.
501. The NCCN Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Search term: ribociclib. Accessed on February 10, 2023.

GnRH – Gonadotropin-releasing hormone.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Koselugo Prior Authorization Policy
- Koselugo™ (selumetinib capsules – AstraZeneca)

REVIEW DATE: 04/12/2023

OVERVIEW

Koselugo, a kinase inhibitor, is indicated for the treatment of pediatric patients ≥ 2 years of age with **neurofibromatosis type 1** (NF1) who have symptomatic, inoperable plexiform neurofibromas.[1]

Koselugo is a mitogen-activated protein kinase kinases 1 and 2 (MEK1/2) inhibitor.[1]

Disease Overview

Neurofibromatoses are a group of tumor suppressor syndromes that predisposes patients to an increased risk of nervous system tumors including neurofibromas, malignant peripheral nerve sheath tumors, and gliomas.[5,6] NF1 is the most common of the neurofibromatoses, occurring in approximately one in 2,500 to 3,000 individuals worldwide.[7,8] NF1 is an autosomal dominant disorder, with 50% of children of affected parents inheriting the mutated NF1 tumor-suppressor gene.[5,7] However, up to 50% of the cases occur spontaneously in patients without a family of NF1.[5-9]

Plexiform neurofibromas are benign nerve sheath tumors that can occur anywhere in the body,[8] affect up to 50% of patients with NF1,[5] and are often present at birth.[7,8] These tumors tend to grow the fastest in the first decade of life,[7,8] and can continue to grow into adolescence and early adulthood.[7] Plexiform neurofibromas may be asymptomatic and only detected with MRI,[5,8] or may cause significant pain,[5,7] disfigurement,[5] bone destruction,[7] and loss of nerve function.[5] Due to the risk of transformation to malignant peripheral nerve sheath tumors, patients with any change in the signs or symptoms of plexiform neurofibromas should be assessed for malignant transformation.[5,8]

Other Uses with Supportive Evidence

In a Phase II, open-label trial, the efficacy of Koselugo was assessed in patients 3 to 21 years of age with recurrent, refractory, or progressive pilocytic astrocytoma with either *KIAA1549-BRAF* fusion or *BRAF V600E* mutation.[2] Koselugo 25 mg/m^2/dose was administered twice daily for up 2 years if the patient did not have progressive disease or unacceptable adverse events. A total of 25 patients were enrolled with a median age of 9.2 years, and 52% were female. A partial response was achieved in 36% of patients, 36% of patients had stable disease, and 28% had disease progression. The 2 year progression-free survival was 70% and 44% of patients have not progressed after a median of 36.4 months of follow-up.

Guidelines

Koselugo is addressed in National Comprehensive Cancer Network (NCCN) guidelines:

- **Central nervous system cancers:** Clinical practice guidelines (version 1.2023 – March 24, 2023) recommend Koselugo for the treatment of recurrent or progressive circumscribed glioma with *BRAF* fusion or *BRAF V600E* activating mutation positive; or neurofibromatosis type 1 mutated glioma, as a single agent.[3,4]
- **Histiocytic Neoplasms:** Clinical practice guidelines (version 1.2022 – May 20, 2022) recommend Koselugo as a single agent for the first-line or subsequent treatment of mitogen-activated protein kinase pathway mutation, no detectable mutation, or testing not available for multisystem

Langerhans cell histocytosis (LCH), single-system lung LCH, multifocal (> 2 lesions) single system bone LCH not responsive to a bisphosphonate, and central nervous system LCH.[10]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Koselugo. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Koselugo is recommended in those who meet the following criteria:

FDA-Approved Indication

134. Neurofibromatosis Type 1. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient meets ONE of the following (i or ii):
  - **i.** Patient is 2 to 18 years of age; OR
  - **ii.** Patient meets both of the following (a and b):
    - **a)** Patient is ≥ 19 years of age; AND
    - **b)** Patient has been previously started on therapy with Koselugo prior to becoming 19 years of age; AND
- **B)** Prior to starting Koselugo, the patient had symptomatic, inoperable plexiform neurofibromas, according to the prescriber.

Other Uses with Supportive Evidence

135. Circumscribed Glioma. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient meets ONE of the following (i or ii):
  - **i.** Patient is 3 to 21 years of age; OR
  - **ii.** Patient meets both of the following (a and b):
    - **a)** Patient is > 21 years of age; AND
    - **b)** Patient has been previously started on therapy with Koselugo prior to becoming 21 years of age; AND
- **B)** Patient has recurrent, refractory, or progressive disease; AND
- **C)** Tumor meets one of the following (i, ii, or iii):
  - **i.** Tumor is *BRAF* fusion positive; OR
  - **ii.** Tumor is *BRAF V600E* activating mutation positive; OR
  - **iii.** Patient has neurofibromatosis type 1 mutated glioma; AND
- **D)** The medication will be used as a single agent.

136. Langerhans Cell Histiocytosis. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient meets one of the following (i, ii, iii, or iv):
  - **i.** Patient meets both of the following (a and b):
    - **a)** Patient has multisystem Langerhans cell histiocytosis; AND
    - **b)** Patient has symptomatic disease or impending organ dysfunction; OR

ii. Patient has single system lung Langerhans cell histiocytosis; OR
iii. Patient meets all of the following (a, b, and c):
a) Patient has single system bone disease; AND
b) Patient has not responded to treatment with a bisphosphonate; AND
Note: Examples of bisphosphonates include pamidronate and zoledronic acid.
c) Patient has more than 2 bone lesions; OR
iv. Patient has central nervous system disease; AND

B) The medication is used as a single agent.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Koselugo is not recommended in the following situations:

348. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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1120. The NCCN Histiocytic Neoplasms Clinical Practice Guidelines in Oncology (version 1.2022 – May 20, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on: April 10, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Krazati Prior Authorization Policy
- Krazati™ (adagrasib tablets – Mirati Therapeutics)

REVIEW DATE: 12/20/2023

OVERVIEW

Krazati, a Kirsten RAt Sarcoma virus (KRAS) inhibitor, is indicated for the treatment of ***KRAS G12C*-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC)**, as determined by an FDA-approved test, in adults who have received at least one prior systemic therapy.[1]
This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of a clinical benefit in a confirmatory trial(s).

Mutations in the *KRAS* gene most commonly occur at codon 12.[2] Data suggest that approximately 30% of patients with NSCLC have *KRAS* mutations. The prognosis of survival of patients with tumors with *KRAS* mutation is poorer compared with that of patients with tumors without *KRAS* mutation.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines recommend Krazati for the following cancer types:

- **Non-Small Cell Lung Cancer:** Guidelines (version 5.2023 – November 8, 2023) recommend Krazati as a subsequent treatment option, for use after at least one prior systemic treatment (i.e., second-line and beyond) if the patient has not received previous *KRAS G12C*-targeted therapy (category 2A). Patients who progressed on Lumakras™ (sotorasib tablets), another *KRAS* inhibitor directed at *KRAS G12C*-mutated NSCLC, should not be treated with Krazati; and vice-versa. The NCCN Central Nervous System Cancers guidelines (version 1.2023 – March 24, 2023) recommend use of Krazati for *KRAS G12C* mutation-positive NSCLC that has metastasized to the brain (category 2A).[3]
- **Colon and Rectal Cancer:** Guidelines for colon cancer (version 4.2023 – November 16, 2023) and rectal cancer (version 6.2023 – November 16, 2023) recommend Krazati for some situations in patients with *KRAS G12C*-mutated disease.[4,5] For initial treatment in combination with Erbitux® (cetuximab intravenous infusion) or Vectibix® (panitumumab intravenous infusion) or as monotherapy if patient is unable to tolerate Erbitux or Vectibix due to toxicity. Krazati is also recommended as subsequent therapy after previous therapy with oxaliplatin, irinotecan, FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Krazati. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Krazati is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Non-Small Cell Lung Cancer (NSCLC).** Approve for 1 year if the patient meets the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has *KRAS G12C*-mutated locally advanced or metastatic NSCLC, as determined by an approved test; AND
   - **C)** Patient has been previously treated with at least one systemic regimen.
     Note: Examples of systemic regimens include those containing one or more of the following products: Keytruda (pembrolizumab intravenous infusion), Opdivo (nivolumab intravenous infusion), Tecentriq (atezolizumab intravenous infusion), Alimta (pemetrexed intravenous infusion), Yervoy (ipilimumab intravenous infusion), Abraxane (albumin-bound paclitaxel intravenous infusion), bevacizumab, cisplatin, carboplatin, docetaxel, gemcitabine, paclitaxel, vinorelbine.

Other Uses with Supportive Evidence

2. **Colon or Rectal Cancer.** Approve for 1 year if the patient meets the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has unresectable, advanced, or metastatic disease; AND
   - **C)** Patient has *KRAS G12C* mutation-positive disease; AND
   - **D)** Patient meets one of the following (i or ii):
     - **i.** The medication is prescribed as part of a combination regimen for colon or rectal cancer; OR
       Note: Examples of combination regimens included Krazati + Erbitux (cetuximab intravenous infusion), Krazati + Vectibix (panitumumab intravenous infusion).
     - **ii.** As per the prescriber, the patient is unable to tolerate combination therapy; AND
   - **E)** Patient has previously received a chemotherapy regimen for colon or rectal cancer.
     Note: Examples of chemotherapy regimens include a fluoropyrimidine such as 5-fluorouracil (5-FU), capecitabine; oxaliplatin, irinotecan, or an adjunctive chemotherapy regimen such as FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Krazati is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Krazati™ tablets [prescribing information]. San Diego, CA: Mirati Therapeutics; December 2022.
2. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 5.2023 - November 8, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 18, 2023.
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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Lapatinib Prior Authorization Policy
- Tykerb® (lapatinib ditosylate tablets – Novartis, generic)

REVIEW DATE: 02/22/2023

OVERVIEW

Lapatinib, a tyrosine kinase inhibitor, is indicated for the following uses:[1]

- **Breast cancer**, in combination with capecitabine tablets for the treatment of patients with **advanced or metastatic disease** whose tumors overexpress human epidermal growth factor receptor 2 (HER2) and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.
  Limitation of Use: Patients should have disease progression on trastuzumab prior to initiation of treatment with lapatinib in combination with capecitabine tablets.
- **Breast cancer**, in combination with letrozole for the treatment of postmenopausal women with **hormone receptor (HR)-positive metastatic disease** that overexpresses HER2 for whom hormonal therapy is indicated. Lapatinib in combination with an aromatase inhibitor (AI) has not been compared with a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer.

Guidelines

Lapatinib is discussed in guidelines from National Comprehensive Cancer Network (NCCN):

- **Breast Cancer:** NCCN guidelines (version 2.2023 – February 7, 2023) recommend lapatinib in combination with trastuzumab (without cytotoxic therapy) or capecitabine for HER2-positive recurrent unresectable (local or regional) or stage IV disease that is HR-negative or HR positive with or without endocrine therapy as fourth-line therapy or beyond (category 2A).[2] Lapatinib is also recommended in combination with an AI with or without trastuzumab for the treatment of recurrent unresectable (local or regional) or Stage IV HR+, HER2+ disease in postmenopausal women or premenopausal women receiving ovarian ablation or suppression (category 2A).[2] Men with breast cancer should be treated similarly to postmenopausal women except that using an AI is ineffective without suppression of testicular steroidogenesis (category 2A). The NCCN clinical practice guidelines on central nervous system cancers (version 2.2022 – September 28, 2022) recommend treatments for patients with brain metastases from breast cancer.[3,4] Capecitabine with lapatinib is recommended as primary treatment in select patients (e.g. patients with small asymptomatic brain metastases), as treatment for recurrent disease or relapsed disease with stable systemic disease or reasonable systemic treatment options.
- **Bone Cancer:** NCCN guidelines (version 2.2023 – September 28, 2022) recommend the use of lapatinib for epidermal growth factor receptor (*EGFR)*-positive recurrent conventional or chondroid chordoma as "Useful In Certain Circumstances" (category 2A).[3,5]
- **Colon or Rectal Cancer:** The NCCN Compendium supports the use of lapatinib in colon or rectal cancer for HER2-amplified, *RAS* and *BRAF* wild-type disease, in combination with trastuzumab, if not previously treated with a HER2 inhibitor.[3]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of lapatinib. All approvals are provided for the duration noted below. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: a woman is defined as an individual with the biological traits of a woman, regardless of the individual's gender identity or gender expression; a man is defined as an individual with the biological traits of a man, regardless of the individual's gender identity or expression.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of lapatinib is recommended in those who meet one of the following criteria:

FDA-Approved Indications

3. Breast Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **C)** Patient has recurrent or metastatic breast cancer; AND
- **D)** Patient meets one of the following criteria (i or ii):
- **i.** Patient meets both of the following criteria (a and b):
  - **a)** The medication will be used in combination with capecitabine or trastuzumab; AND
  - **b)** Patient has tried at least three prior anti-HER2 based regimens; OR
    Note: Examples of anti-HER2 regimens include: Perjeta (pertuzumab intravenous infusion) + trastuzumab + docetaxel, Perjeta + trastuzumab + paclitaxel; Enhertu (fam-trastuzumab deruxtecan-nxki intravenous infusion); Kadcyla (ado-trastuzumab emtansine intravenous infusion); Tukysa (tucatinib tablet) + trastuzumab + capecitabine.
- **ii.** The medication will be used in combination with an aromatase inhibitor (that is, letrozole, anastrozole, or exemestane) AND patient meets the following criteria (a and b):
  - **a)** Patient has hormone receptor-positive (HR+) [i.e., estrogen receptor positive {ER+}- and/or progesterone receptor positive {PR+}]disease; AND
  - **b)** One of the following ([1] [2] or [3]) applies:
    - **(1)** Patient is a postmenopausal woman*; OR
    - **(2)** Patient is a premenopausal or perimenopausal woman* and is receiving ovarian suppression/ablation with a gonadotropin-releasing hormone (GnRH) agonist, surgical bilateral oophorectomy, or ovarian irradiation; OR
      Note: Examples of a GnRH agonist include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous injection).
    - **(3)** Patient is a man* and is receiving a gonadotropin-releasing hormone (GnRH) analog.
      Note: Examples of a GnRH analog include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Firmagon (degarelix acetate subcutaneous injection), Orgovyx (relugolix tablet).

***** Refer to the Policy Statement.

Other Uses with Supportive Evidence

2. **Bone Cancer.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has recurrent chordoma; AND
   - **C)** Patient has epidermal growth-factor receptor (*EGFR*)-positive disease.

3. **Colon or Rectal Cancer.** Approve for 1 year if the patient meets the following criteria (A, B, C, D, E, F, and G)
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has unresectable, advanced, or metastatic disease; AND
   - **C)** Patient has human epidermal receptor 2 (HER2)-amplified disease; AND
   - **D)** Patient has wild-type *RAS* and *BRAF* disease; AND
   - **E)** Patient meets ONE of the following (i or ii):
     - **i.** Patient has tried at least one chemotherapy regimen; OR
       Note: Examples of chemotherapy are fluoropyrimidine such as 5-fluorouracil (5-FU), capecitabine; oxaliplatin, irinotecan, or an adjunctive chemotherapy regimen such as FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).
     - **ii.** Patient is not a candidate for intensive therapy, according to the prescriber; AND
   - **F)** The medication is used in combination with trastuzumab; AND
   - **G)** Patient has not been previously treated with a HER2-inhibitor.
     Note: Examples of HER2-inhibitors are trastuzumab products, Nerlynx (neratinib tablets), Kadcyla (ado-trastuzumab emtansine intravenous infusion) Perjeta (pertuzumab intravenous infusion), Enhertu (fam-trastuzumab deruxtecan-nxki intravenous infusion).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of lapatinib is not recommended in the following situations:

1. **Head and Neck, Squamous Cell Carcinoma.** In one Phase III study in 688 patients with squamous cell carcinoma of the head and neck, adding lapatinib to chemoradiotherapy and as maintenance monotherapy was not more effective than placebo in improving disease-free survival or overall survival.[6]

2. **Urothelial Carcinoma.** In one Phase III trial, 232 patients with HER1/HER2 metastatic urothelial bladder cancer who did not have progressive disease during chemotherapy were randomized to receive lapatinib or placebo after completing first-line or initial chemotherapy.[7] Median progression-free survival was the primary endpoint, for lapatinib and placebo was 4.5 months and 5.1 months respectively; no statistically significant difference was detected between the two group.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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6 Harrington K, Temam S, Mehanna H, et al. Postoperative adjuvant lapatinib and concurrent chemoradiotherapy followed by maintenance lapatinib monotherapy in high-risk patients with resected squamous cell carcinoma of the head and neck: a phase III, randomized, double-blind, placebo-controlled study. *J Clin Oncol*. 2015;33:4202-4209
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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Lenalidomide Prior Authorization Policy
- Revlimid® (lenalidomide capsules – Celgene, generic)

REVIEW DATE: 05/10/2023

OVERVIEW

Lenalidomide, a thalidomide analog, is indicated for the following uses in adults:[1]
- **Follicular lymphoma**, previously treated, in combination with a rituximab product.
- **Mantle cell lymphoma**, in patients whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib subcutaneous or intravenous bolus injection).
- **Marginal zone lymphoma**, previously treated, in combination with a rituximab product.
- **Multiple myeloma**, as maintenance following autologous hematopoietic stem cell transplantation.
- **Multiple myeloma**, treatment, in combination with dexamethasone.
- **Myelodysplastic syndrome**, for transfusion-dependent anemia due to low- or intermediate-risk disease, associated with a deletion 5q abnormality with or without cytogenetic abnormalities.

A limitation of use with lenalidomide is that it is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia outside of controlled clinical trials.[1]

Guidelines

Lenalidomide is incorporated into various guidelines by the National Comprehensive Cancer Network (NCCN).[2-11]

- **B-Cell Lymphomas:** The NCCN guidelines for B-Cell lymphomas (version 2.2023 – February 8, 2023), discuss therapeutic options for diffuse large B-cell lymphoma (DLBCL), the most common type of other B-cell lymphoma.[2] Lenalidomide, with or without rituximab, is mentioned as a second-line therapy as "useful in certain circumstances" (category 2A). Monjuvi® (tafasitamab-cxix intravenous infusion) plus lenalidomide is recommended as a preferred regimen in second-line therapy (category 2A). Many examples of first-line therapies are recommended (e.g., RCHOP [rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone] {category 1}, dose-adjusted EPOCH [etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin] + rituximab [category 2A]). One example of a first-line therapy for patients with poor left ventricular function or in those who are frail is RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisone). NCCN also recommends optional first-line consolidation therapy of lenalidomide maintenance (category 2B) for patients 60 to 80 years of age. Other types of B-cell lymphomas (high grade B-cell lymphomas [not otherwise specified], post-transplant lymphoproliferative disorders, acquired immunodeficiency [AIDS]-related B-cell lymphomas, high-grade B-cell lymphomas with translocations of MYC and BCL2 and/or BCL6 [double/triple hit lymphoma]) are also cited in the guidelines and note a place in therapy of lenalidomide. Regimens recommended in these clinical scenarios are similar to those used in DLBCL.
    - **Castleman's Disease:** Lenalidomide is recommended as an option as second-line and subsequent therapy, with or without rituximab, for multi-centric Castleman's disease that is relapsed/refractory or progressive disease.[2]
    - **Follicular Lymphomas:** Lenalidomide plus rituximab is a first-line recommended therapy (category 2A). Many second-line and subsequent therapies are listed, usually with or without rituximab. Lenalidomide with Gazyva® (obinutuzumab intravenous infusion) is an "other recommended regimen" in this setting (category 2A).

- **Mantle Cell Lymphoma:** Lenalidomide, in combination with rituximab, is recommended as a preferred, less aggressive induction therapy (category 2A). Lenalidomide with rituximab is recommended as a preferred second-line and subsequent therapy (category 2A). The regimen of lenalidomide, rituximab, and Imbruvica is cited as and second-line and subsequent therapy that is useful in certain circumstances (category 2A).
- **Marginal Zone Lymphoma:** Lenalidomide plus rituximab has a category 2B recommendation for first-line therapy as an "other recommended regimen" and a category 2A recommendation for second-line and subsequent therapy as a "preferred regimen".

- **Central Nervous System (CNS) Cancers:** The NCCN guidelines for CNS cancers (version 1.2023 – March 24, 2023) recommend lenalidomide, with or without rituximab, as one of the options for patients with relapsed or refractory disease.[3]
- **Histiocytic Neoplasms:** The NCCN guidelines for histiocytic neoplasms (version 1.2022 – May 20, 2022) recommend lenalidomide for Langerhans cell histiocytosis as first-line or as subsequent therapy for single system multifocal skin disease (including mucosa) and for relapsed/refractory disease (category 2A).[4]
- **Hodgkin Lymphoma:** The NCCN Hodgkin lymphoma guidelines (version 2.2023 – November 8, 2022) recommend lenalidomide as a subsequent option for treatment of classical Hodgkin lymphoma as a single agent for refractory or relapsed disease in patients ≥ 18 years of age (category 2A) who have tried at least three prior lines of therapy. Many other therapies are recommended as primary systemic therapy regimens before lenalidomide is recommended.[5]
- **Kaposi Sarcoma:** The NCCN guidelines for Kaposi sarcoma (version 1.2023 – December 20, 2022) recommended lenalidomide as an agent "useful under certain conditions" for subsequent systemic therapy options for relapsed/refractory advanced cutaneous, oral, visceral or nodal disease that has progressed on or not responded to first-line systemic therapy and progressed on alternative first-line systemic therapy (category 2A).[9] This includes use when given alone (in patients without human immunodeficiency virus [HIV]) or with antiretroviral therapy for patients with HIV. First-line systemic therapy options include liposomal doxorubicin (preferred) and paclitaxel. Other subsequent systemic therapy options for relapsed/refractory therapy are also cited (e.g., Pomalyst® [pomalidomide capsules] {preferred}, Thalomid® [thalidomide capsules], imatinib).
- **Multiple Myeloma:** The NCCN guidelines for multiple myeloma (version 3.2023 – December 8, 2022) feature lenalidomide prominently in a variety of scenarios with several category 1 recommendations (e.g., lenalidomide with dexamethasone for other recommended regimens for primary therapy, monotherapy for maintenance therapy).[6] The agent is also cited in other regimens with category 2A and 2B recommendations. Lenalidomide is also indicated for treatment in combination with dexamethasone for the management of POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome as induction therapy for transplant eligible patients and for transplant ineligible patients (category 2A).
- **Myelodysplastic Syndrome (MDS):** The NCCN guidelines for MDS (version 1.2023 – September 12, 2022) recommend lenalidomide in a variety of clinical scenarios among patients with symptomatic anemia both with and without 5q deletion abnormalities (category 2A).[7]
- **Myeloproliferative Neoplasms:** The NCCN has guidelines regarding myeloproliferative neoplasms (version 3.2022 – August 11, 2022) discuss myelofibrosis with related anemia.[8] Lenalidomide is recommended in the management of anemia associated with myelofibrosis (useful in certain circumstances), with or without prednisone, for a variety of clinical scenarios (category 2A) including patients with erythropoietin levels ≥ 500 mU/mL and with erythropoietin levels < 500 mU/mL and no response or loss of response to erythropoietic stimulating agents.
- **Systemic Light Chain Amyloidosis:** The NCCN guidelines for systemic light chain amyloidosis (version 2.2023 – November 28, 2022) cite lenalidomide as a therapeutic option used in combination dexamethasone, and in some circumstances with additional medications, in several clinical scenarios, including as primary therapy (category 2A).[10] Also, lenalidomide in

combination with dexamethasone, and an additional medication recommended in some situations, is also recommended in patients with previously treated disease (category 2A).

- **T-Cell Lymphomas:** The NCCN guidelines for T-cell lymphomas (version 1.2023 – January 5, 2023) make several recommendations that include lenalidomide.[11] Lenalidomide is recommended as a second-line and subsequent therapy for adult T-cell leukemia/lymphoma (category 2A). For peripheral T-cell lymphomas, lenalidomide is recommended as second-line and subsequent therapy (other recommended regimens) as a monotherapy (category 2A). Indications regarding peripheral T-cell lymphomas include the following: peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma; enteropathy-associated T-cell lymphoma; monomorphic epitheliotropic intestinal T-cell lymphoma; nodal peripheral T-cell lymphoma with T-follicular helper (TFH) phenotype; follicular T-cell lymphoma; and hepatosplenic gamma-delta T-cell lymphomas. Other regimens are recommended as first-line or preferred in both of these clinical scenarios.

Safety

In a prospective randomized clinical study in the first-line treatment of patients with CLL, use of lenalidomide as a single agent increased the risk of death compared with chlorambucil given as a single agent.[1] Lenalidomide is only available through the lenalidomide Risk Evaluation Mitigation Strategy program. Males and females must follow the required reproductive precautions.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of lenalidomide. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of lenalidomide is recommended in those who meet the one of following criteria:

FDA-Approved Indications

1. **Follicular Lymphoma.** Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets one of the following (i or ii)
     - **i.** Patient is using lenalidomide in combination with rituximab; OR
     - **ii.** Patient has tried at least one other regimen.
       Note: Examples include bendamustine plus Gazyva (obinutuzumab intravenous infusion) or rituximab; bendamustine plus Gazyva; CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) plus Gazyva or rituximab; CVP (cyclophosphamide, vincristine, prednisone) plus Gazyva or rituximab; chlorambucil with or without rituximab; cyclophosphamide with or without rituximab; rituximab; Gazyva; or Aliqopa (copanlisib intravenous infusion).

2. **Mantle Cell Lymphoma**. Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets one of the following (i or ii).
     - **i.** Patient is using lenalidomide in combination with rituximab; OR
     - **ii.** Patient has tried at least two other regimens.
       Note: Examples include HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab; the

NORDIC regimen (dose-intensified induction immunochemotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone alternating with rituximab and high-dose cytarabine); RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone); bendamustine injection plus rituximab; RDHA (rituximab, dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin); Imbruvica (ibrutinib capsules, tablets, and oral suspension) with or without rituximab; Calquence (acalabrutinib tablets and capsules); or Brukinsa (zanubrutinib capsules).

3. **Marginal Zone Lymphoma.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets one of the following (i or ii).
      i. Patient is using lenalidomide in combination with rituximab; OR
      ii. Patient has tried least one other regimen.
      Note: Examples include CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab; bendamustine + rituximab; CVP (cyclophosphamide, vincristine, prednisone) + rituximab; rituximab; chlorambucil with or without rituximab; cyclophosphamide with or without rituximab; bendamustine + Gazyva (obinutuzumab intravenous infusion); Copiktra (duvelisib capsules); Aliqopa (copanlisib intravenous infusion); or Zydelig (idelalisib capsules).

4. **Multiple Myeloma.** Approve for 1 year if the patient is ≥ 18 years of age.

5. **Myelodysplastic Syndrome.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets one of the following (i, ii, or iii):
      i. Patient has symptomatic anemia; OR
      ii. Patient has transfusion-dependent anemia; OR
      iii. Patient has anemia that is not controlled with an erythropoiesis-stimulating agent
      Note: Examples include Epogen/Procrit (epoetin alfa injection), Aranesp (darbepoetin alfa injection).

Other Uses with Supportive Evidence

6. **B-Cell-Lymphomas (Other):** Approve for 1 year if the patient meets the following criteria (A and B):
   Note: Examples include diffuse large B-cell lymphoma (DLBCL); high grade B-cell lymphomas (not otherwise specified), post-transplant lymphoproliferative disorders, AIDS-related B-cell lymphomas, high-grade B-cell lymphomas with translocations of MYC and BCL2 and/or BCL6 (double/triple hit lymphoma).
   A) Patient is ≥ 18 years of age; AND
   B) Patient has tried at least one other regimen.
   Note: Examples include RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone); dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab; RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine); DHA (dexamethasone, cytarabine) plus platinum (carboplatin, cisplatin, oxaliplatin) ± rituximab; ICE (Ifex, carboplatin, etoposide) ± rituximab; RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisone); GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab or gemcitabine, dexamethasone, carboplatin) ± rituximab; R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine); or bendamustine ± rituximab.

7. **Castleman's Disease.** Approve for 1 year in patients with relapsed/refractory or progressive disease.

8. **Central Nervous System Lymphoma.** Approve for 1 year if according to the prescriber the patient has relapsed or refractory disease.

9. **Hodgkin Lymphoma, Classical.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has tried at least three other regimens.
   Note: Examples include ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine); BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone); Adcetris (brentuximab vedotin intravenous infusion); Adcetris + AVD (doxorubicin, vinblastine, and dacarbazine); DHAP (dexamethasone, cisplatin, high-dose cytarabine); ICE (ifosfamide, carboplatin, etoposide); or GVD (gemcitabine, vinorelbine, liposomal doxorubicin).

10. **Kaposi Sarcoma.** Approve for 1 year if the patient meets the following (A and B):
    A) Patient has relapsed or refractory disease; AND
    B) Patient has tried at least one other medication; AND
    Note: Examples include liposomal doxorubicin, paclitaxel, Pomalyst (pomalidomide capsules), Thalomid (thalidomide capsules), and imatinib.

11. **Langerhans Cell Histiocytosis:** Approve for 1 year for patients with multifocal skin disease.

12. **Myelofibrosis.** Approve for 1 year if the patient meets the following (A or B):
    A) Patient meets the following (i, ii, and iii):
       i. Patient is ≥ 18 years of age; AND
       ii. According to the prescriber the patient has anemia; AND
       iii. Patient has serum erythropoietin levels ≥ 500 mU/mL.
    B) Patient meets the following (i, ii, iii, and iv):
       i. Patient is ≥ 18 years of age; AND
       ii. According to the prescriber the patient has anemia; AND
       iii. Patient has serum erythropoietin levels < 500 mU/mL; AND
       iv. Patient has experienced no response or loss of response to an erythropoiesis-stimulating agent.

13. **Peripheral T-Cell Lymphomas.** Approve for 1 year if the patient meets the following (A and B):
    Note: Indications regarding peripheral T-cell lymphomas include peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL); enteropathy-associated T-cell lymphoma (EATL); monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL); nodal peripheral T-cell lymphoma (nodal PTCL) with T-follicular helper (TFH) phenotype; follicular T-cell lymphoma (FTCL); and hepatosplenic gamma-delta T-cell lymphomas.
    A) Patient is ≥ 18 years of age; AND
    B) Patient has tried at least one other regimen.
    Note: Examples of regimens include Beleodaq (belinostat intravenous infusion); Adcetris (brentuximab vedotin intravenous infusion); DHAP (dexamethasone, cisplatin, cytarabine); ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin); GDP (gemcitabine, dexamethasone, cisplatin); GemOX (gemcitabine, oxaliplatin); ICE (ifosfamide, carboplatin, etoposide); or Istodax (romidepsin intravenous infusion).

14. **POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) Syndrome.** Approve for 1 year if the patient meets the following (A and B):
    A) Patient is ≥ 18 years of age; AND

B) Use of lenalidomide is in combination with dexamethasone.

15. Systemic Light Chain Amyloidosis. Approve for 1 year if the patient meets the following (A and B):
A) Patient is ≥ 18 years of age; AND
B) Use of lenalidomide is in combination with dexamethasone.

16. T-Cell Leukemia/Lymphoma. Approve for 1 year if the patient meets the following (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient has tried at least one other regimen.
Note: Examples include Adcetris (brentuximab vedotin intravenous infusion) plus CHP (cyclophosphamide, doxorubicin, and prednisone); CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone); CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone); dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin); HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine; or Beleodaq (belinostat intravenous infusion).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of lenalidomide is not recommended in the following situations:

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Lenvima Prior Authorization Policy
- Lenvima® (lenvatinib capsules – Eisai)

REVIEW DATE: 06/07/2023

OVERVIEW

Lenvima, a kinase inhibitor, is indicated for the following uses:[1]

- **Differentiated thyroid cancer** for treatment of locally recurrent or metastatic, progressive, radioactive iodine refractory disease.
- **Endometrial cancer**, in combination with Keytruda® (pembrolizumab intravenous infusion), for advanced disease that is mismatch repair proficient (pMMR), as determined by an FDA-approved test, or not microsatellite instability-high (MSI-H) who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.
- **Hepatocellular carcinoma** for first-line treatment of patients with unresectable disease.
- **Renal cell carcinoma**, advanced in combination with everolimus tablets, following one prior anti-angiogenic therapy.
- **Renal cell carcinoma,** advanced, for first-line treatment of adult patients in combination with Keytruda.

Guidelines

Lenvima is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):[2]

- **Hepatocellular Carcinoma**: NCCN guidelines (version 1.2023 – March 10, 2023) recommend Lenvima as "other recommended regimen" for first-line systemic therapy (Child-Pugh Class A only) for hepatocellular carcinoma (category 1). It is also recommended as subsequent-line therapy upon disease progression (Child-Pugh Class A only) [category 2A].[3]
- **Kidney Cancer**: NCCN guidelines (version 4.2023 – January 18, 2023) recommend Lenvima + everolimus as a "preferred regimen" as subsequent therapy for relapse or stage IV disease with clear cell histology (category 2A); this combination is also listed as systemic therapy, "other recommended regimens", for relapsed or stage IV disease for non-clear cell histology (category 2A). Lenvima + Keytruda is listed as a "preferred regimen" for first-line therapy for relapsed or stage IV disease for clear cell histology (category 1); this combination is also listed as "other recommended regimen" for subsequent therapy for relapsed or stage IV with clear cell histology (category 2A).[4]
- **Melanoma**: **Cutaneous**: NCCN guidelines (version 2.2023 – March 10, 2023) recommend use of Lenvima + Keytruda (category 2A) for metastatic or unresectable disease, as second-line or subsequent therapy after treatment with anti-programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) -based therapy, including in combination with anti-CTL antigen 4 (CTLA-4) for at least two doses.[8]
- **Thymomas and Thymic Carcinomas**: NCCN guidelines (version 1.2023 – December 15, 2022) recommend single-agent Lenvima (category 2A) as second-line systemic therapy for thymic carcinoma.[5]
- **Thyroid Carcinoma**: NCCN guidelines (version 2.2023 – May 18, 2023) indicate that first-line treatment for differentiated thyroid cancer is surgery, whenever possible, followed by radioactive iodine therapy in selected patients, and levothyroxine therapy in all patients.[2] Systemic therapy options include cytotoxic chemotherapy and kinase inhibitors. The guidelines state that for progressive and/or symptomatic disease, Lenvima is a preferred systemic therapy regimen

(category 1) for locally recurrent, advanced, and/or metastatic disease not amenable to radioactive iodine therapy. There is a footnote that states that kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. Lenvima can be considered for treatment of progressive or symptomatic medullary thyroid disease if clinical trials or preferred systemic therapy options are not available or appropriate, or if there is progression on preferred systemic therapy options (category 2A).[6]

- **Uterine Neoplasms**: NCCN guidelines (version 2.2023– April 28, 2023) recommends Lenvima with Keytruda combination therapy for biomarker directed systemic therapy for second-line treatment for recurrent or metastatic endometrial carcinoma for non-MSI-high [MSI-H]/non-MMR-deficient [dMMR] tumors. This combination is a category 1 recommendation as preferred therapy.[7]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lenvima. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lenvima is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Endometrial Carcinoma**. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND
   - **C)** The medication is used in combination with Keytruda (pembrolizumab intravenous injection); AND
   - **D)** Patient has tried at least one systemic therapy; AND
     Note: Examples of systemic therapy include carboplatin, paclitaxel, docetaxel, cisplatin, doxorubicin, or ifosfamide.
   - **E)** Patient is not a candidate for curative surgery or radiation.

2. **Hepatocellular Cancer**. Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has unresectable or metastatic disease.

3. **Renal Cell Cancer**. Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has advanced disease; AND
   - **C)** Patient meets ONE of the following (i or ii):
     - **i.** Lenvima is being used in combination with Keytruda (pembrolizumab intravenous infusion); OR
     - **ii.** Lenvima is being used in combination with everolimus tablets/Afinitor Disperz (everolimus tablets for oral suspension) AND patient meets one of the following (a or b):
     - **a)** Patient has clear cell histology and patient has tried one antiangiogenic therapy; OR

Note: Examples of antiangiogenic therapy include Inlyta (axitinib tablets), Votrient (pazopanib tablets), sunitinib, or Cabometyx (cabozantinib tablets).

b) Patient has non-clear cell histology.

4. Thyroid Carcinoma, Differentiated. Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) Patient is ≥ 18 years of age; AND

B) Patient has differentiated thyroid carcinoma.
Note: Examples of differentiated thyroid carcinoma include papillary, follicular, and oncocytic carcinoma (formerly Hürthle cell carcinoma).

C) The disease is refractory to radioactive iodine therapy.

Other Uses with Supportive Evidence

5. Melanoma. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient has unresectable or metastatic melanoma; AND

C) The medication is used in combination with Keytruda (pembrolizumab intravenous injection); AND

D) Patient has disease progression on anti-programmed death receptor-1 (PD-1)/programmed death-ligand 1 (PD-L1)-based therapy.
Note: Examples of anti-PD-1/PD-L1 therapies include Opdivo (nivolumab intravenous infusion) + Yervoy (ipilimumab intravenous infusion), Opdualag (nivolumab and relatlimab-rmbw intravenous infusion), Keytruda, Opdivo.

6. Thymic Carcinoma. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient is ≥ 18 years of age; AND

B) Patient has tried at least one chemotherapy regimen.
Note: Examples of a chemotherapy regimen include carboplatin plus paclitaxel, cisplatin, doxorubicin plus cyclophosphamide, cisplatin plus etoposide.

7. Thyroid Carcinoma, Medullary. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient is ≥ 18 years of age; AND

B) Patient has tried at least one systemic therapy.
Note: Examples of systemic therapy include Caprelsa (vandetanib tablets), Cometriq (cabozantinib capsules), Retevmo (selpercatinib capsules), and Gavreto (pralsetinib capsules).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lenvima is not recommended in the following situations:

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Lenvima® capsules [prescribing information]. Woodcliff Lake, NJ: Eisai; November 2022.
2. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 5, 2023. Search term: lenvatinib.
3. The NCCN Hepatocellular Carcinoma Clinical Practice Guidelines in Oncology (version 1.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 06, 2023.
4. The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – January 18, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 5, 2023.
5. The NCCN Thymomas and Thymic Carcinoma Clinical Practice Guidelines in Oncology (version 1.2023 – December 15, 2022). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 5, 2023.
6. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (version 2.2023 – May 18, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 5, 2023.
7. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (version 2.2023 – April 28, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 5, 2023.
8. The NCCN Melanoma: Cutaneous Clinical Practice Guidelines in Oncology (version 2.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 6, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Lonsurf Prior Authorization Policy
- Lonsurf® (trifluridine and tipiracil tablets – Taiho Oncology)

REVIEW DATE: 02/15/2023

OVERVIEW

Lonsurf, a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor, is indicated for the following uses:[1]

- **Colorectal cancer**, metastatic, in adults who have been previously treated with oxaliplatin-, fluoropyrimidine-, and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor (VEGF) biological therapy, and if *RAS* wild-type, an anti-epidermal growth factor receptor (EGFR) therapy.
- **Gastric or gastroesophageal junction adenocarcinoma**, metastatic, in adults previously treated with at least two lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, human epidermal growth factor receptor 2 (HER2)/neu-targeted therapy.

Guidelines

Lonsurf is addressed in National Comprehensive Cancer Network guidelines:

- **Colon cancer** (version 3.2022 – January 25, 2023) and **rectal cancer** (version 4.2022 – January 25, 2023) guidelines recommend Lonsurf as subsequent therapy as a single agent or in combination with bevacizumab for advanced or metastatic disease not previously treated with Lonsurf. This recommendation is for patients who have progressed through all available regimens, besides Lonsurf or Stivarga® (regorafenib tablets) with or without bevacizumab.[2,3,6]
- **Gastric cancer** (version 2.2022 – January 11, 2022), and **esophageal and esophagogastric cancer** (version 5.2022 – December 5, 2022) guidelines recommend Lonsurf as a single agent for third line or subsequent therapy for locoregional disease in patients who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic gastric and esophagogastric junction adenocarcinoma and Karnofsky performance score ≥ 60% or Eastern Cooperative Oncology Group performance status of ≤ 2 (category 1).[4-6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lonsurf. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lonsurf is recommended in those who meet one of the following criteria:

FDA-Approved Indications

17. Colon, Rectal, or Appendiceal Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):

A) Patient has been previously treated with a fluoropyrimidine (e.g., capecitabine, 5-fluorouracil [5-FU]); AND
B) Patient has been previously treated with oxaliplatin; AND
C) Patient has been previously treated with irinotecan; AND
D) If the patient's tumor or metastases are wild-type *RAS* (*KRAS* wild-type and *NRAS* wild-type) [that is, the tumors or metastases are *KRAS* and *NRAS* mutation negative], Erbitux (cetuximab intravenous infusion) or Vectibix (panitumumab intravenous infusion) has been tried.

2. **Gastric or Gastroesophageal Junction Adenocarcinoma.** Approve for 1 year if the patient has been previously treated with at least two chemotherapy regimens for gastric or gastroesophageal junction adenocarcinoma (e.g., regimens containing one or more of the following agents: capecitabine, 5-fluorouracil [5-FU], oxaliplatin, paclitaxel, docetaxel, and irinotecan).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lonsurf is not recommended in the following situations:

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Lonsurf® tablets [prescribing information]. Princeton, NJ: Taiho Oncology; December 2019.
2. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 3.2022 – January 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on: February 7, 2023.
3. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 4.2022 – January 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on: February 7, 2023.
4. The NCCN Gastric Cancer Clinical Practice Guidelines in Oncology (version 2.2022 – January 11, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on: February 7, 2023.
5. The NCCN Esophageal and Esophagogastric Junction Cancers Clinical Practice Guidelines in Oncology (version 5.2022 – December 5, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on: February 7, 2023.
6. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 7, 2023. Search term: trifluridine/tipiracil.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Lorbrena Prior Authorization Policy
- Lorbrena® (lorlatinib tablets – Pfizer)

REVIEW DATE: 11/29/2023

OVERVIEW

Lorbrena, a kinase inhibitor, is indicated for the treatment of metastatic **non-small cell lung cancer** (NSCLC) in adults whose tumors are anaplastic lymphoma kinase (*ALK*)-positive as detected by an FDA-approved test.[1]

GUIDELINES

Lorbrena is addressed in National Comprehensive Cancer Network (NCCN) guidelines:[2-5]

- **Histiocytic Neoplasms:** Guidelines (version 1.2023 – August 11, 2023) recommend Lorbrena as a "useful in certain circumstances" treatment option for *ALK*-positive Erdheim-Chester disease (category 2A).[3]
- **NSCLC:** Guidelines (version 5.2023 – November 8, 2023) recommend testing for biomarkers (e.g., *ALK* rearrangement, *ROS* proto-oncogene 1 (*ROS1)* gene rearrangement) in eligible patients with NSCLC.[4]
  - *ALK*-rearrangement-positive NSCLC: If *ALK* rearrangement is discovered prior to first-line systemic therapy, Lorbrena is a preferred first-line treatment option (category 1). If *ALK* rearrangement is discovered during first-line systemic therapy, options are to complete the planned systemic therapy (including maintenance therapy) or to interrupt the systemic therapy and treat with Lorbrena (preferred, category 2A) or another ALK inhibitor. Lorbrena is also recommended for patients who progress on other *ALK* inhibitors (category 2A).
  - *ROS* proto-oncogene 1 *(ROS1)* rearrangement-positive NSCLC: Lorbrena is a recommended subsequent therapy (category 2A) for patients who progress on Zykadia® (ceritinib capsules and tablets), Xalkori® (crizotinib capsules), or Rozlytrek™ (entrectinib capsules). Lorbrena is not a recommended first-line treatment option for *ROS1* rearrangement-positive NSCLC.
- **Inflammatory Myofibroblastic Tumor (IMT):** NCCN Soft Tissue Sarcoma guidelines (version 2.2023 – April 25, 2023) and NCCN Uterine Neoplasms guidelines (version 1.2023 – December 22, 2022) recommend Lorbrena as a treatment option for IMT with *ALK* translocation.[5,6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lorbrena. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lorbrena is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. **Non-Small Cell Lung Cancer – Anaplastic Lymphoma Kinase (*ALK*)-Positive.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has advanced or metastatic disease; AND
   - **C)** Patient has anaplastic lymphoma kinase (*ALK*)-positive disease; AND
   - **D)** The mutation was detected by an approved test.

Other uses With Supportive Evidence

2. **Erdheim-Chester Disease**. Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has anaplastic lymphoma kinase (*ALK*) rearrangement/fusion-positive disease.

3. **Inflammatory Myofibroblastic Tumor.** Approve for 1 year if the patients meets the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has anaplastic lymphoma kinase (*ALK*)-positive disease; AND.
   - **C)** Patient meets one of the following criteria (i or ii):
     - **i.** Patient has advanced, recurrent, or metastatic disease; OR
     - **ii.** The tumor is inoperable.

4. **Non-Small Cell Lung Cancer – *ROS1* Rearrangement-Positive.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has advanced or metastatic disease; AND
   - **C)** Patient has *ROS1* rearrangement-positive disease; AND
   - **D)** Patient has tried at least one of Xalkori (crizotinib capsules), Zykadia (ceritinib capsules or tablets), or Rozlytrek (entrectinib capsules).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lorbrena is not recommended in the following situations:

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

12. Lorbrena® tablets [prescribing information]. New York, NY: Pfizer; March 2021.
13. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 27, 2023. Search term: lorlatinib.
14. The NCCN Histiocytic Neoplasms Clinical Practice Guidelines in Oncology (version 1.2023 – August 11, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 27, 2023.
15. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 5.2023 - November 8, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 27, 2023.
16. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 27, 2023.
17. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (version 1.2024 – September 20, 2023) © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 27, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Lumakras Prior Authorization Policy
- Lumakras™ (sotorasib tablets – Amgen)

REVIEW DATE: 06/14/2023

OVERVIEW

Lumakras, a kirsten rat sarcoma (KRAS) inhibitor, is indicated for the treatment of adults with ***KRAS G12C*-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC)**, as determined by an FDA-approved test, who have received at least one prior systemic therapy.[1]

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Mutations in the *KRAS* gene most commonly occur at codon 12.[2] Data suggest that approximately 25% of patients with adenocarcinomas in a North American population have *KRAS* mutations. The prognosis of survival of patients with tumors with *KRAS* mutation is poorer compared with that of patients with tumors without *KRAS* mutation.

Guidelines

Lumakras is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):

- **Non-Small Cell Lung Cancer:** NCCN guidelines (version 3.2023 – April 13, 2023) recommend Lumakras as a subsequent therapy for patients with metastatic NSCLC with the *KRAS G12C* mutation (category 2A) who have been previously treated with combination chemotherapy regimens (± immunotherapy).[2]
- **Pancreatic Adenocarcinoma:** NCCN guidelines (version 1.2023 – May 4, 2023) recommend Lumakras as a subsequent therapy (category 2A) under "useful in certain circumstances" for locally advanced or metastatic disease. It is also recommended therapy for local recurrence in the pancreatic operative bed after resection (category 2A).[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lumakras. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lumakras is recommended in those who meet the following criteria:

FDA-Approved Indication

4. **Non-Small Cell Lung Cancer (NSCLC).** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   D) Patient is ≥ 18 years of age; AND
   E) Patient has *KRAS G12C*-mutated locally advanced or metastatic NSCLC, as determined by an approved test; AND
   F) Patient has been previously treated with at least one systemic regimen.
   Note: Examples of systemic regimens include those containing one or more of the following products: Keytruda (pembrolizumab intravenous infusion), Opdivo (nivolumab intravenous infusion), Tecentriq (atezolizumab intravenous infusion), Alimta (pemetrexed intravenous infusion), Yervoy (ipilimumab intravenous infusion), Abraxane (albumin-bound paclitaxel intravenous infusion), bevacizumab, cisplatin, carboplatin, docetaxel, gemcitabine, paclitaxel, vinorelbine.

Other Uses with Supportive Evidence

5. **Pancreatic Adenocarcinoma.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has *KRAS G12C*-mutated disease, as determined by an approved test; AND
   C) Patient meets one of the following (i or ii):
      i. Patient meets both of the following (a and b):
         a) Patient has locally advanced or metastatic disease; AND
         b) Patient has been previously treated with at least one systemic regimen; OR
         Note: Examples of systemic regimens include one or more of the following: gemcitabine, albumin-bound paclitaxel, capecitabine, Keytruda (pembrolizumab intravenous infusion), FOLFIRINOX (5-fluoruracil + leucovorin + irinotecan + oxaliplatin).
      ii. Patient has recurrent disease after resection.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lumakras is not recommended in the following situations:

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

6. Lumakras™ tablets [prescribing information]. Thousand Oaks, CA: Amgen; April 2023.
7. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – April 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 12, 2023.
8. The NCCN Pancreatic Adenocarcinoma Clinical Practice Guidelines in Oncology (version 1.2023 – May 4, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 12, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Lynparza Prior Authorization Policy
- Lynparza® (olaparib tablets – AstraZeneca)

REVIEW DATE: 02/22/2023; selected revision 06/07/2023

OVERVIEW

Lynparza, a poly (ADP-ribose) polymerase (PARP) inhibitor, is indicated for the following uses:[1]

- **Breast cancer**, with deleterious or suspected deleterious germline BReast Cancer (g*BRCA*) mutated, human epidermal growth factor 2 (HER2)-negative metastatic disease, in adults who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with hormone receptor-positive (HR+) breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy.
- **Breast cancer**, for the adjuvant treatment of deleterious or suspected deleterious g*BRCA* mutated HER2-negative high-risk early breast cancer in adults who have been treated with neoadjuvant or adjuvant chemotherapy.
- **Ovarian cancer, maintenance** treatment of deleterious or suspected deleterious germline or somatic *BRCA* mutated recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, in adults who are in a complete or partial response to platinum-based chemotherapy.
- **Ovarian cancer, maintenance** treatment of deleterious or suspected deleterious *gBRCA* or somatic *BRCA*-mutated advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer in adults who are in complete or partial response to first-line platinum-based chemotherapy.
- **Ovarian cancer, maintenance treatment in combination** with bevacizumab for advanced epithelial ovarian, fallopian tube or primary peritoneal cancer in adults who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either: a deleterious or suspected deleterious *BRCA* mutation, and/or genomic instability.
- **Pancreatic adenocarcinoma,** maintenance treatment of deleterious or suspected deleterious g*BRCA* mutated metastatic disease, in adults whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.
- **Prostate cancer**, for the treatment of deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration resistant prostate cancer (mCRPC) in adults who have progressed following prior treatment with Xtandi® (enzalutamide tablets) or abiraterone.
- **Prostate cancer,** for the treatment of deleterious or suspected deleterious *BRCA*-mutated (*BRCA*m) mCRPC, in combination with abiraterone and prednisone or prednisolone in adults.

Guidelines

Lynparza is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):[7]

- **Breast Cancer:** NCCN guidelines (version 2.2023 – February 7, 2023) list single-agent Lynparza as a "Preferred Regimen" for first-line therapy for patients with a germline *BRCA 1/2* mutation for recurrent, unresectable, or stage IV HR-positive, HER2-negative disease, with visceral crisis or that is endocrine therapy-refractory (category 1).[2] For triple negative breast cancer with germline *BRCA*1/2 mutation, Lynparza is listed as a "Preferred Regimen" as first-line and second-line therapy for patients with programmed cell death ligand 1 combined positive score (PD-L1 CPS) < 10 (category 1). There is a footnote which states PARP inhibitors can be considered for a later line for those with *BRCA*1/2 mutation (category 2A); however, available evidence suggests it is more

effective if used earlier. Lynparza is also recommended as a single-agent for recurrent, unresectable, or stage IV HER2-positive disease with a *BRCA*1/2 mutation (category 2A). It is noted that although Lynparza is FDA-approved for HER2-negative disease, the NCCN panel supports use in any breast cancer subtype with a *BRCA1* or *BRCA2* mutation. The guidelines also state that addition of 1 year of adjuvant Lynparza is an option for select patients with germline *BRCA*1/2 mutation after completion of adjuvant chemotherapy for the following scenarios: triple negative disease if patient has ≥ primary tumor (pT2) or ≥ pathologic lymph nodes (pN1) disease after adjuvant chemotherapy or patient has residual disease after preoperative chemotherapy (category 1); HR+, HER2-negative tumors if 1) ≥ 4 positive lymph nodes after adjuvant chemotherapy (category 2A) or 2) residual disease after preoperative therapy and a clinical stage, pathologic stage, estrogen receptor status, and tumor grade (CPS+EG) score ≥ 3 (category 2A). The guidelines state that adjuvant Lynparza therapy can be given with endocrine therapy.

- **Ovarian Cancer**: NCCN guidelines (version 1.2023 – December 22, 2022) recommend Lynparza for maintenance therapy after primary treatment in patients who have had a complete or partial response in the following situations: single-agent Lynparza for *BRCA*1/2 mutations (category 1 if bevacizumab was not used during primary therapy and category 2A if bevacizumab was used during primary therapy); Lynparza + bevacizumab if bevacizumab was used as part of primary therapy (*BRCA*1/2 wild-type or unknown and homologous recombination deficient [category 1]; germline/somatic *BRCA*1/2 mutation [category 1]).[3] The guidelines recommend use of Zejula® (niraparib capsules), Rubraca® (rucaparib tablets), or Lynparza as single-agent maintenance therapy options in patients with platinum-sensitive persistent or recurrent disease who have completed two or more lines of platinum-based therapy and are in complete or partial response for BRCA mutation ("Preferred"; category 1); Lynparza can be used in this setting without a BRCA mutation (category 2A). The guidelines recommend Lynparza as single-agent targeted therapy for treatment of patients with deleterious germline *BRCA* mutated advanced (persistent disease or recurrence) ovarian cancer following two or more lines of chemotherapy (category 3).
- **Pancreatic Cancer:** NCCN guidelines (version 2.2022 – December 6, 2022) recommend Lynparza as a "Preferred Regimen" maintenance therapy for metastatic disease after the patient has tried first-line platinum-based chemotherapy.[4] It is specifically recommended in patients who have germline *BRCA1/2* mutations and who have not had disease progression after at least 4 to 6 months of chemotherapy (category 2A).
- **Prostate Cancer:** NCCN guidelines (version 1.2023 – September 16, 2022) recommend Lynparza as "Useful in Certain Circumstances" for mCRPC with germline or somatic HRR mutation for patients who have received prior novel hormone therapy (i.e. abiraterone, Xtandi® [enzalutamide capsule or tablet], Nubeqa® [darolutamide tablet], or Erleada® [apalutamide tablet]) [category 1; category 2B if the patient has visceral metastases and has tried docetaxel].[5] A footnote notes that Lynparza is a treatment option for patients with mCRPC and a pathogenic mutation (germline and/or somatic) in a HRR gene (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L)*, who have been previously treated with androgen receptor-directed therapy. However, efficacy appears to be driven by the cohort of patients with at least one alteration in *BRCA2*, *BRCA1*, or *ATM*, and in particular by patients with *BRCA2* or *BRCA1* mutations based on exploratory gene-by-gene analysis. There may be heterogeneity of response to Lynparza for non-*BRCA* mutations based on the specific gene mutation.
- **Uterine Neoplasms:** NCCN guidelines (version 1.2023 – December 22, 2022) state that Lynparza may be considered as a single-agent second-line therapy as "Useful in Certain Circumstances", for *BRCA2*-altered uterine leiomyosarcoma (category 2A).[6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lynparza. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lynparza is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Breast Cancer – Adjuvant Therapy.** Approve for 1 year (total) if the patient meets the following criteria (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has germline *BRCA* mutation-positive breast cancer; AND
   - **C)** Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
   - **D)** Patient has tried neoadjuvant or adjuvant therapy.

2. **Breast Cancer – Recurrent or Metastatic Disease.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has recurrent or metastatic disease; AND
   - **C)** Patient has germline *BRCA* mutation-positive breast cancer.

3. **Ovarian, Fallopian Tube, or Primary Peritoneal Cancer – Maintenance, Monotherapy.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets ONE of the following criteria (i or ii):
     - **i.** Patient meets both of the following criteria for first-line maintenance therapy (a and b):
       - **a)** Patient has a germline or somatic *BRCA* mutation-positive disease as confirmed by an approved test; AND
       - **b)** Patient is in complete or partial response to first-line platinum-based chemotherapy regimen; OR
         Note: Examples are carboplatin with paclitaxel, carboplatin with doxorubicin, docetaxel with carboplatin.
     - **ii.** Patient is in complete or partial response after at least two platinum-based chemotherapy regimens.
       Note: Examples of platinum-based chemotherapy are carboplatin with gemcitabine, carboplatin with paclitaxel, cisplatin with gemcitabine.

4. **Ovarian, Fallopian Tube, or Primary Peritoneal Cancer – Maintenance, Combination Therapy.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** The medication is used in combination with bevacizumab; AND
   - **C)** Patient has homologous recombination deficiency (HRD)-positive disease as confirmed by an approved test; AND
     Note: HRD-positive disease includes patients with *BRCA* mutation-positive disease.
   - **D)** Patient is in complete or partial response to first-line platinum-based chemotherapy regimen.
     Note: Examples of chemotherapy regimens are carboplatin with paclitaxel, carboplatin with doxorubicin, docetaxel with carboplatin.

5. **Pancreatic Cancer – Maintenance Therapy.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has a germline *BRCA* mutation-positive metastatic disease; AND
   C) The disease has not progressed on at least 16 weeks of treatment with a first-line platinum-based chemotherapy regimen.

6. **Prostate Cancer.** Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has metastatic castration resistant prostate cancer; AND
   C) Patient meets one of the following criteria (i or ii):
      i. The medication is used concurrently with a gonadotropin-releasing hormone (GnRH) analog; OR
      Note: Examples are leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Vantas (histrelin acetate subcutaneous implant), Firmagon (degarelix acetate subcutaneous injection), Orgovyx (relugolix tablets).
      ii. Patient has had a bilateral orchiectomy; AND
   D) Patient meets the following criteria (i or ii):
      i. Patient meets the following criteria (a and b):
         a) Patient has germline or somatic homologous recombination repair (HRR) gene-mutated disease, as confirmed by an approved test; AND
         Note: HRR gene mutations include *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*.
         b) Patient has been previously treated with at least one androgen receptor-directed therapy; OR
         Note: Androgen-receptor-directed therapy includes: abiraterone, Xtandi (enzalutamide capsules and tablets), Nubeqa (darolutamide tablets), or Erleada (apalutamide tablets).
      ii. Patient meets the following criteria (a and b):
         a) Patient has a *BRCA* mutation; AND
         b) The medication is used in combination with abiraterone plus one of prednisone or prednisolone.

Other Uses With Supportive Evidence:

7. **Ovarian Cancer – Treatment.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   Note: This also includes fallopian tube, or primary peritoneal cancer.
   A) Patient is ≥ 18 years of age; AND
   B) Patient has a germline *BRCA*-mutation as confirmed by an approved test; AND
   C) Patient has progressed on two or more prior lines of chemotherapy.

8. **Uterine Leiomyosarcoma**. Approve for 1 year if the patient meets the following criteria (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has *BRCA2*-altered disease; AND
   C) Patient has tried one systemic regimen.

Note: Examples of a systemic regimen include one or more of the following products: dacarbazine, docetaxel, doxorubicin, epirubicin, gemcitabine, ifosfamide Yondelis (trabectedin intravenous infusion).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lynparza is not recommended in the following situations:

8. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

7. Lynparza® tablets [prescribing information]. Wilmington, DE: AstraZeneca; October 2022.
8. The NCCN Ovarian Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 20, 2023.
9. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – February 7, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 20, 2023.
10. The NCCN Pancreatic Adenocarcinoma Clinical Practice Guidelines in Oncology (version 2.2022 – December 6, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 20, 2023.
11. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – September 16, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed February 20, 2023.
12. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2023). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed February 20, 2023.
13. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 20, 2023. Search term: olaparib.

BRCA – BReast CAncer; HER2 – Human epidermal growth factor receptor 2; GnRH – Gonadotropin-releasing hormone; HR+ – hormone receptor positive; ER+ – estrogen receptor positive; PR+ – progesterone-receptor positive; NCCN – National Comprehensive Cancer Network.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Lytgobi Prior Authorization Policy
- Lytgobi® (futibatinib tablets – Taiho Oncology)

REVIEW DATE: 11/08/2023

OVERVIEW

Lytgobi, a fibroblast growth factor receptor 2 (*FGFR2*) inhibitor, is indicated for the treatment of adults with previously treated, unresectable, locally advanced or metastatic intrahepatic **cholangiocarcinoma** harboring *FGFR2* gene fusions or other rearrangements.

Guidelines

Lytgobi is addressed in National Comprehensive Cancer Network (NCCN) guidelines:

- **Biliary Tract Cancers:** NCCN guidelines (version 2.2023 – May 10, 2023) recommend Lytgobi for disease progression on or following systemic therapy for patients with unresectable or metastatic intrahepatic or extrahepatic cholangiocarcinoma with *FGFR2* fusions or rearrangements.[2,3] NCCN guidelines also recommend Pemazyre® (pemigatinib tablets) for the same indication.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lytgobi. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lytgobi is recommended in those who meet the following criteria:

FDA-Approved Indication

18. Cholangiocarcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has unresectable locally advanced or metastatic disease; AND
- **C)** Tumor has fibroblast growth factor receptor 2 (*FGFR2*) gene fusions or other rearrangements, as detected by an approved test; AND
- **D)** Patient has been previously treated with at least one systemic regimen.
  Note: Examples of systemic regimens include gemcitabine + cisplatin, 5-fluorouracil + oxaliplatin or cisplatin, capecitabine + cisplatin or oxaliplatin, gemcitabine + Abraxane (albumin-bound paclitaxel) or capecitabine or oxaliplatin, and gemcitabine + cisplatin + Abraxane.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lytgobi is not recommended in the following situations:

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

18. Lytgobi® tablets [prescribing information.]. Princeton, NJ: Taiho Oncology; September 2022.
19. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 6, 2023. Search term: futibatinib.
20. The NCCN Biliary Tract Cancers Clinical Practice Guidelines in Oncology (version 2.2023 – May 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 6, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Mekinist Prior Authorization Policy
- Mekinist® (trametinib tablets and oral solution – Novartis)

REVIEW DATE: 04/05/2023; selected revision 09/13/2023

OVERVIEW

Mekinist, a kinase inhibitor, is indicated for the treatment of patients with the following conditions:[1]

- **Low-grade glioma,** in combination with Tafinlar, for the treatment of pediatric patients ≥ 1 year of age with a *BRAF V600E* mutation who require systemic therapy.
- **Melanoma**, in the following situations:
  - As a single agent for unresectable or metastatic disease with a *BRAF V600E* or *V600K* mutation as detected by an FDA-approved test.
  - In combination with Tafinlar® (dabrafenib capsules and tablets for oral suspension), for unresectable or metastatic disease with a *BRAF V600E* or *V600K* mutation as detected by an FDA-approved test.
  - In combination with Tafinlar, as adjuvant treatment of *BRAF V600E* or *V600K* mutation-positive disease as detected by an FDA-approved test, with involvement of lymph nodes, following complete resection.
- **Non-small cell lung cancer**, in combination with Tafinlar, for disease that has the *BRAF V600E* mutation as detected by an FDA-approved test.
- **Solid tumors – unresectable or metastatic**, in combination with Tafinlar, for *BRAF V600E* mutation-positive disease, as determined by an FDA-approved test, in patients ≥ 1 year of age who have no satisfactory alternative treatment options.
- **Thyroid cancer**, in combination with Tafinlar, for locally advanced or metastatic anaplastic disease with *BRAF V600E* mutation and with no satisfactory locoregional treatment options.

Limitations of Use: Mekinist is not indicated for treatment of patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition.

Dosing: For the tablet dosage form, Mekinist has dosing for patients who are adults and for patients who are between 6 and 17 years of age and weigh ≥ 26 kg. The oral solution dosage form also has weight-based dosing for patients ≥ 8 kg.

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines support use of Mekinist in multiple cancers.

- **Central Nervous System Cancers**: Guidelines (version 1.2023 – March 24, 2023) recommend a BRAF/MEK inhibitor combination (i.e., Tafinlar/Mekinist or Zelboraf® [vemurafenib tablets]/Cotellic® [cobimetinib tablets]) for treatment of *BRAF V600E* activation mutations in adults in the following situations: adjuvant treatment of pilocytic astrocytoma, pleomorphic xanthoastrocytoma, or ganglioglioma; recurrent or progressive low-grade glioma, oliogdenroglioma, or isocitrate dehydrogenase-2 (*IDH2*)-mutant astrocytoma; and recurrent glioblastoma.[7] BRAF/MEK combination therapy is also recommended for melanoma with brain metastases. Guidelines for pediatric central nervous system (CNS) cancers (version 2.2023 – October 31, 2022) include targeted therapy with Tafinlar + Mekinist as adjuvant therapy or for recurrent or progressive disease, if the cancer has a *BRAF V600E* mutation.[9]

- **Histiocytic Neoplasms:** Guidelines (version 1.2022 – May 20, 2022) recommend Cotellic as "preferred" or Mekinist as "other recommended regimen" for histiocytic neoplasms (if there is a MAP kinase pathway mutation, or no detectable mutation, or testing is not available) for the following types: Langerhans cell histiocytosis (including multisystem, pulmonary or central nervous system lesions), Erdheim-Chester disease, and Rosai-Dorfman disease.[6]
- **Melanoma, Cutaneous:** Guidelines (version 2.2023 – March 10, 2023) recommend BRAF/MEK inhibitor combinations among the "preferred" therapies for first-line and subsequent treatment of metastatic or unresectable melanoma with a *V600*-activating mutation.[2] While combination BRAF/MEK inhibition is preferred, if a combination is contraindicated, monotherapy with a BRAF inhibitor is an option. Tafinlar + Mekinist is also recommended in guidelines as adjuvant therapy (including for nodal recurrence) in some patients with Stage III disease, including use post-surgery or use after complete lymph node dissection. If unacceptable toxicity to Tafinlar/Mekinist, other BRAF/MEK combinations can be considered.
- **Non-Small Cell Lung Cancer:** Guidelines (version 2.2023 – February 17, 2023) list Tafinlar + Mekinist among the first-line therapy and subsequent therapy options for tumors with a *BRAF* mutation.[3] NCCN also notes that monotherapy with a BRAF inhibitor (Tafinlar or Zelboraf) is a treatment option when combination therapy is not tolerated.

The NCCN Compendium[8] recommends use of Mekinist, in combination with Tafinlar, for the following *BRAF V600* positive tumors (all category 2A): High-grade gliomas, ampullary adenocarcinoma, neuroendocrine tumors, pancreatic adenocarcinoma, salivary gland tumors, esophageal and esophagogastric junction cancers, gastric cancer, biliary tract cancers, gastrointestinal stromal tumors, brain metastases due to melanoma, ovarian cancer, and differentiated thyroid carcinoma. NCCN Compendium also recommends use of Tafinlar as monotherapy for low-grade serous ovarian cancer.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Mekinist. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mekinist is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Low Grade Glioma.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   - **A)** Patient is ≥ 1 year of age; AND
   - **B)** Patient has *BRAF V600* mutation-positive disease; AND
   - **C)** The medication will be taken in combination with Tafinlar (dabrafenib capsules or tablets for oral suspension); AND
   - **D)** Patient requires systemic therapy.

2. **Melanoma.** Approve for 1 year if the patient meets the following (A, B, and C):
   - **A)** Patient is ≥ 6 years of age; AND
   - **B)** Patient has unresectable, advanced (including Stage III or Stage IV disease), or metastatic melanoma; AND

Note: This includes adjuvant treatment in patients with Stage III disease with no evidence of disease post-surgery.

C) Patient has *BRAF V600* mutation-positive disease.

3. **Non-Small Cell Lung Cancer.** Approve for 1 year if the patient meets the following (A, B, and C):
   A) Patient is ≥ 6 years of age; AND
   B) Patient has *BRAF V600* mutation-positive disease; AND
   C) The medication is prescribed in combination with Tafinlar (dabrafenib capsules or tablets for oral suspension).

4. **Solid Tumors – Unresectable or Metastatic.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   Note: Examples of solid tumors are: biliary tract cancer, brain metastases due to melanoma, high-grade gliomas, differentiated thyroid carcinoma, gastrointestinal stromal tumors, gastric cancer, esophageal and esophagogastric junction cancers, salivary gland tumors, pancreatic adenocarcinoma, neuroendocrine tumors, and ampullary adenocarcinoma.
   A) Patient is ≥ 1 year of age; AND
   B) Patient has *BRAF V600* mutation-positive disease; AND
   C) The medication will be taken in combination with Tafinlar (dabrafenib capsules or tablets for oral suspension); AND
   D) According to the prescriber, the patient has no satisfactory alternative treatment options.

5. **Thyroid Carcinoma, Anaplastic.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   A) Patient is ≥ 6 years of age; AND
   B) Patient has locally advanced or metastatic anaplastic disease; AND
   C) Patient has *BRAF V600* mutation-positive disease; AND
   D) The medication is prescribed in combination with Tafinlar (dabrafenib capsules or tablets for oral suspension), unless intolerant.

Other Uses with Supportive Evidence

6. **Histiocytic Neoplasm.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 6 years of age; AND
   B) Patient meets one of the following (i, ii, or iii):
      i. Patient has Langerhans cell histiocytosis and one of the following (a, b, or c):
         a) Multisystem disease; OR
         b) Pulmonary disease; OR
         c) Central nervous system lesions; OR
      ii. Patient has Erdheim-Chester disease; OR
      iii. Patient has Rosai-Dorfman disease.

7. **Ovarian, Fallopian Tube, or Primary Peritoneal Cancer**. Approve for 1 year if the patient meets the following (A, B, and C):
   - **A)** Patient is ≥ 6 years of age; AND
   - **B)** Patient has recurrent disease; AND
   - **C)** Patient meets ONE of the following (i or ii):
     - **i.** The medication is used for low-grade serous carcinoma; OR
     - **ii.** The patient meets both of the following (a and b):
       - **a)** Patient has *BRAF V600* mutation-positive disease; AND
       - **b)** The medication will be taken in combination with Tafinlar (dabrafenib capsules or tablets for oral suspension).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mekinist is not recommended in the following situations:

1. **Colon or Rectal Cancer.** Mekinist is not indicated for treatment of patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition.[1]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

14. Mekinist® tablets and oral solution [prescribing information]. East Hanover, NJ: Novartis; August 2023.
15. The NCCN Melanoma: Cutaneous Clinical Practice Guidelines in Oncology (version 2.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on April 3, 2023.
16. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – February 17, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on April 3, 2023.
17. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (version 1.2023 – March 24, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on April 3, 2023.
18. The NCCN Ovarian Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on April 3, 2023.
19. The NCCN Histiocytic Neoplasms Clinical Practice Guidelines in Oncology (version 1.2022 – May 20, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on April 3, 2023.
20. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 1.2023 – March 24, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on April 3, 2023.
21. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 3, 2023. Search term: trametinib.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Mektovi Prior Authorization Policy
- Mektovi® (binimetinib tablets – Array BioPharma)

REVIEW DATE: 07/19/2023; selected revision 10/18/2023

OVERVIEW

Mektovi, a kinase inhibitor, is indicated for the following uses:[1]

- **Melanoma,** in combination with Braftovi® (encorafenib capsules) for the treatment of patients with unresectable or metastatic disease with a *BRAF V600E* or *V600K* mutation as detected by an FDA-approved test.
- **Non-small cell lung cancer (NSCLC),** in combination with Braftovi, for the treatment of adult patients with metastatic NSCLC with a *BRAF V600E* mutation, as detected by an FDA-approved test.

Guidelines

National Comprehensive Cancer Network guidelines support use of Mektovi in the following cancers.

- **Histiocytic Neoplasms:** Guidelines (version 1.2022 – May 20, 2022) recommend Cotellic® (cobimetinib tablets) "preferred" or Mektovi as "other recommended regimen" for histiocytic neoplasms (if there is a MAP kinase pathway mutation, or no detectable mutation, or testing is not available) for the following types: Langerhans cell histiocytosis (including multisystem, pulmonary, or central nervous system lesions).[3]
- **Melanoma, Cutaneous:** Guidelines (version 2.2023 – March 10, 2023) recommend BRAF/MEK inhibitor combinations among the "preferred" therapies for first-line and subsequent treatment of metastatic or unresectable melanoma with a *V600* activating mutation.[2] This combination is also recommended for adjuvant treatment (category 2B). Mektovi as a single agent is a category 2B recommendation for NRAS-mutated tumors (for progression following immune checkpoint inhibitor therapy). While combination BRAF/MEK inhibition is preferred, if a combination is contraindicated, monotherapy with a BRAF inhibitor is an option, especially in patients who are not appropriate candidates for checkpoint immunotherapy.
- **Non-Small Cell Lung Cancer:** Guidelines (version 3.2023 – April 13, 2023) recommend Tafinlar® (dabrafenib capsules) + Mekinist® (trametinib tablets) for first-line "preferred" and subsequent therapy (both category 2A) for *BRAF V600E* mutation-positive disease.[4] Zelboraf® (vemurafenib tablets) or Tafinlar monotherapy is also recommended under "useful in certain circumstances" (both category 2A). Braftovi + Mektovi combination is not yet addressed in the guidelines.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Mektovi. All approvals are provided the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mektovi is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Melanoma.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   - **D)** Patient is ≥ 18 years of age; AND
   - **E)** Patient has unresectable, advanced, or metastatic melanoma; AND
   - **F)** Patient has *BRAF V600* mutation-positive disease; AND
   - **G)** The medication will be used in combination with Braftovi (encorafenib capsules).

2. **Non-Small Cell Lung Cancer.** Approve for 1 year if the patient meets the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has *BRAF V600E* mutation-positive metastatic disease; AND
   - **C)** The medication will be taken in combination with Braftovi (encorafenib capsules).

Other Uses with Supportive Evidence

3. **Histiocytic Neoplasm.** Approve for 1 year if the patient meets the following (A and B):
   - **C)** Patient is ≥ 18 years of age; AND
   - **D)** Patient has Langerhans cell histiocytosis and one of the following (i, ii, or iii):
     - **ii.** Multisystem disease; OR
     - **iii.** Pulmonary disease; OR
     - **iv.** Central nervous system lesions.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mektovi is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

22. Mektovi® tablets [prescribing information]. Boulder, CO: Array BioPharma; October 2023.
23. The NCCN Melanoma Clinical Practice Guidelines in Oncology (version 2.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on July 14, 2023.
24. The NCCN Histiocytic Neoplasms Clinical Practice Guidelines in Oncology (version 1.2022 – May 20, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on July 14, 2023.
25. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – April 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on October 16, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Nerlynx Prior Authorization Policy
- Nerlynx® (neratinib tablets – Puma)

REVIEW DATE: 10/18/2023

OVERVIEW

Nerlynx, a kinase inhibitor, is indicated in adults for the following uses:[1]
- Early-stage human epidermal growth factor receptor 2 (HER2)-positive **breast cancer**, as a single agent for extended adjuvant therapy to follow adjuvant trastuzumab-based therapy.
- Advanced or metastatic HER2-positive **breast cancer**, in combination with capecitabine, for patients who have received two or more prior anti-HER2-based regimens in the metastatic setting.

Guidelines

Nerlynx is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):
- **Breast cancer:** Guidelines (version 4.2023 – March 23, 2023) note that Nerlynx can be considered as extended adjuvant therapy following adjuvant trastuzumab-containing therapy in patients with hormone receptor (HR)-positive, HER2-positive disease with a perceived high risk of recurrence (category 2A).[2] The benefits or toxicities associated with extended Nerlynx in patients who have received Perjeta® (pertuzumab intravenous infusion) or Kadcyla® (ado-trastuzumab emtansine intravenous infusion) are unknown. For the treatment of recurrent unresectable (local or regional) or Stage IV or metastatic HER2 positive disease, Nerlynx + capecitabine is recommended for fourth-line and beyond setting (category 2A).
- **Central nervous system cancers**: Guidelines (version 1.2023 – March 24, 2023) list Nerlynx + capecitabine (category 2A) and Nerlynx + paclitaxel (category 2B) for brain metastases for patients with HER2 positive breast cancer.[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Nerlynx. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nerlynx is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Breast Cancer – Adjuvant Therapy.** Approve for 1 year (total) if the patient meets the following (A, B, C, and D):
   A) Patient is ≥ 18 years of age; AND
   B) Patient will not be using this medication in combination with human epidermal growth factor 2 (HER2) antagonists.
   Note: Examples of HER2 antagonists are trastuzumab and Perjeta (pertuzumab intravenous infusion).

C) Patient has HER2-positive breast cancer; AND
D) Patient meets ONE of the following (i or ii):
  i. The medication is requested for extended adjuvant therapy after the patient has completed 1 year of adjuvant therapy with a trastuzumab intravenous product; OR
  ii. Patient has tried adjuvant therapy with a trastuzumab intravenous product and could not tolerate 1 year of therapy, according to the prescriber.

2. Breast Cancer – Recurrent or Metastatic Disease. Approve for 1 year if the patient meets the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has human epidermal growth factor receptor 2 (HER2)-positive breast cancer; AND
C) The medication is used in combination with capecitabine; AND
D) Patient has tried at least two prior anti-HER2 based regimens.
Note: Examples include Perjeta (pertuzumab intravenous infusion) + trastuzumab + docetaxel, Perjeta + trastuzumab + paclitaxel; Enhertu (fam-trastuzumab deruxtecan-nxki intravenous infusion), Kadcyla (ado-trastuzumab emtansine intravenous infusion), Tukysa (tucatinib tablets) + trastuzumab + capecitabine, trastuzumab + capecitabine, lapatinib + capecitabine, trastuzumab + lapatinib.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nerlynx is not recommended in the following situations:

10. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

26. Nerlynx® tablets [prescribing information]. Los Angeles, CA: Puma; March 2022.
27. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – March 23, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 17, 2023.
28. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 1.2023 – March 24, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 17, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Nilutamide Prior Authorization Policy
- Nilandron® (nilutamide tablets – Concordia, generic)

REVIEW DATE: 01/18/2023

OVERVIEW

Nilutamide, in combination with surgical castration, is indicated for the treatment of **metastatic prostate cancer (Stage D_2)**.[1] For maximum benefit, nilutamide treatment must begin on the same day as or on the day after surgical castration.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for **prostate cancer** (version 1.2023 – September 16, 2022) recommend nilutamide in combination with luteinizing hormone-releasing hormone agonists [Lupron® (leuprolide subcutaneous injection), Lupron Depot® (leuprolide acetate intramuscular injection), Trelstar® (triptorelin pamoate intramuscular injection), Zoladex® (goserelin acetate subcutaneous implant), Vantas® (histrelin acetate subcutaneous implant)] with or without external beam radiation therapy for androgen deprivation therapy.[2,3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of nilutamide. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of nilutamide is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Prostate Cancer.** Approve for 1 year if nilutamide is used concurrently with a luteinizing hormone-releasing hormone (LHRH) agonist.
   Note: Examples are Lupron (leuprolide subcutaneous injection), Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Vantas (histrelin acetate subcutaneous implant).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of nilutamide is not recommended in the following situations:

11. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Nilandron® [prescribing information]. St. Michael, Barbados: Concordia; May 2017.
2. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – September 16, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed January 17, 2023.
3. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed January 17, 2023. Search term: nilutamide.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Ninlaro Prior Authorization Policy
- Ninlaro® (ixazomib capsules – Takeda)

REVIEW DATE: 04/12/2023

OVERVIEW

Ninlaro, an oral proteasome inhibitor, is indicated in combination with lenalidomide and dexamethasone for treatment of patients with **multiple myeloma** who have received at least one prior therapy.[1]

Limitations of Use: Ninlaro is not recommended for use in the maintenance setting or in newly diagnosed multiple myeloma in combination with lenalidomide and dexamethasone outside of controlled clinical trials. Ninlaro should be taken once a week on the same day and at approximately the same time for the first 3 weeks of a 4-week cycle. There are dose modification guidelines which are recommended to manage treatment-related adverse events, including platelet count, absolute neutrophil count (ANC), and other toxicities (e.g., rash, peripheral neuropathy). Treatment should be continued until disease progression or unacceptable toxicity. Safety and efficacy are not established in patients < 18 years of age.

Guidelines

Ninlaro is discussed in various guidelines from the National Comprehensive Cancer Network (NCCN).

- **Multiple Myeloma:** NCCN guidelines (version 3.2023 – December 8, 2022) list multiple therapeutic regimens that may be used for primary therapy and previously treated multiple myeloma.[2] For primary therapy, in transplant candidates, Ninlaro/cyclophosphamide/dexamethasone (category 2A) and Ninlaro/lenalidomide/dexamethasone (category 2B) are listed under "Useful in certain circumstances". Ninlaro/lenalidomide/dexamethasone is a category 2A recommendation for non-transplant candidates under "Other recommended regimens". Maintenance with Ninlaro is also listed among the alternatives for transplant and non-transplant candidates (category 2B for both settings). For previously treated disease, multiple regimens are listed, including Ninlaro/lenalidomide/dexamethasone (preferred, category 1), Ninlaro/Pomalyst (pomalidomide capsules)/dexamethasone (preferred for "Bortezomib-refractory" group), and Ninlaro/cyclophosphamide/dexamethasone under "Other recommended regimens for early relapses (1-3 prior therapies).
- **Systemic Light Chain Amyloidosis:** NCCN guidelines (version 2.2022 – November 28, 2022) list Ninlaro ± dexamethasone and Ninlaro/lenalidomide/dexamethasone among the treatment options for patients with previously treated disease (both category 2A).[3]
- **Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma:** NCCN guidelines (version 1.2023 – July 6, 2022) list Ninlaro/rituximab/dexamethasone (category 2A) among the treatment options for primary therapy and for previously treated disease.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ninlaro. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ninlaro is recommended in those who meet the following criteria:

FDA-Approved Indication

2. Multiple Myeloma. Approve for 1 year if the patient meets BOTH of the following (A and B):
- **B)** Patient is ≥ 18 years of age; AND
- **C)** Patient meets one of the following (i, ii, or iii):
  - **i.** Ninlaro will be taken in combination with lenalidomide or cyclophosphamide and dexamethasone; OR
  - **ii.** Patient has received at least ONE prior regimen for multiple myeloma; OR
    Note: Examples include regimens containing bortezomib, cyclophosphamide, Kyprolis (carfilzomib intravenous infusion), lenalidomide, Darzalex (daratumumab intravenous infusion).
  - **iii.** The medication will be used following autologous stem cell transplantation (ASCT).

Other Uses with Supportive Evidence

3. Systemic Light Chain Amyloidosis. Approve for 1 year if the patient meets BOTH of the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has tried at least one other regimen for this condition.
  Note: Examples of agents used in other regimens include bortezomib, lenalidomide, cyclophosphamide, and melphalan.

4. Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma. Approve for 1 year if the patient meets BOTH of the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The medication is used in combination with a rituximab product and dexamethasone.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ninlaro is not recommended in the following situations:

12. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

21. Ninlaro® capsules [prescribing information]. Cambridge, MA: Takeda; April 2022.
22. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 3.2023 – December 8, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 30, 2023.
23. The NCCN Systemic Light Chain Amyloidosis Clinical Practice Guidelines in Oncology (version 2.2023 – November 28, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 30, 2023.
24. The NCCN Waldenstrom Macroglobulinemia/Lymphoblastic Lymphoma Clinical Practice Guidelines in Oncology (version 1.2023 – July 6, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 30, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Nubeqa Prior Authorization Policy
- Nubeqa® (darolutamide tablets – Bayer)

REVIEW DATE: 07/19/2023

OVERVIEW

Nubeqa, an androgen receptor inhibitor, is indicated for the treatment of adults for the following uses:[1]
- **Prostate cancer, metastatic, hormone-sensitive**, in combination with docetaxel.
- **Prostate cancer, non-metastatic, castration-resistant**.

Guidelines

According to the National Comprehensive Cancer Network guidelines for **prostate cancer** (version 1.2023 – September 16, 2022), for non-metastatic, castration-resistant prostate cancer, androgen deprivation therapy is continued to maintain castrate serum levels of testosterone (< 50 ng/dL).[2] Nubeqa, Erleada™ (apalutamide tablets) and Xtandi® (enzalutamide tablets and capsules) are all category 1 preferred regimens if the prostate specific antigen doubling time is ≤ 10 months. For metastatic castration naïve prostate cancer, the guidelines recommend abiraterone, Xtandi, Erleada, and docetaxel as preferred agents (category 1).

Dosing

For patients with hormone-sensitive metastatic prostate cancer, treated with Nubeqa in combination with docetaxel, the first of the 6 cycles of docetaxel should be administered within 6 weeks after the start of Nubeqa.[1] Treatment with Nubeqa may be continued until disease progression or unacceptable toxicity, even if a cycle of docetaxel is delayed, interrupted, or discontinued. Patients receiving Nubeqa should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or have had a bilateral orchiectomy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Nubeqa. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nubeqa is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Prostate Cancer – Metastatic, Castration-Sensitive.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets one of the following (i or ii):
     - **i.** The medication is used concurrently with docetaxel; OR
     - **ii.** Patient has completed docetaxel therapy; AND
   - **C)** Patient meets ONE of the following (i, ii, or iii):

i. The medication is used concurrently with a gonadotropin-releasing hormone (GnRH) agonist; OR

Note: Examples of GnRH agonists include: leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Vantas (histrelin acetate subcutaneous implant).

ii. The medication is used concurrently with Firmagon (degarelix subcutaneous injection); OR

iii. Patient has had a bilateral orchiectomy.

2. Prostate Cancer – Non-Metastatic, Castration-Resistant. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient is ≥ 18 years of age; AND

B) Patient meets one of the following (i, ii, or iii):

i. The medication is used concurrently with a gonadotropin-releasing hormone (GnRH) agonist; OR

Note: Examples of GnRH agonists include: leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Vantas (histrelin acetate subcutaneous implant).

ii. The medication is used concurrently with Firmagon (degarelix subcutaneous injection); OR

iii. Patient has had a bilateral orchiectomy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nubeqa is not recommended in the following situations:

13. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

4. Nubeqa® tablets [prescribing information]. Whippany, NJ: Bayer; August 2022.
5. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – September 16, 2022). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 17, 2023.
6. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 16, 2023. Search term: darolutamide.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Odomzo Prior Authorization Policy
- Odomzo® (sonidegib capsules – Novartis)

REVIEW DATE: 12/21/2022

OVERVIEW

Odomzo, a hedgehog pathway inhibitor, is indicated for the treatment of adults with locally advanced **basal cell carcinoma** that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy.[1]

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines for basal cell carcinoma (version 2.2022 – March 24, 2022) note that surgical approaches offer the most effective and efficient means for accomplishing a cure; radiation therapy may be chosen as the primary treatment in order to achieve optimal overall results.[2] For locally advanced disease in which curative radiation therapy and curative surgery are not feasible, a hedgehog pathway inhibitor such as Odomzo is among the treatment options (category 2A). For primary or recurrent nodal metastases, Odomzo (category 2B) is among the alternatives when surgery is not feasible.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Odomzo. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Odomzo is recommended in those who meet one of the following criteria:

FDA-Approved Indication

5. Basal Cell Carcinoma, Locally Advanced. Approve for 1 year if the patients meets ONE of the following conditions (A or B):

D) Initial Therapy. Approve if the patient meets BOTH of the following (i and ii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient meets one of the following (a or b):
  - ~~(1)~~ Patient has recurrent basal cell carcinoma following surgery or radiation therapy; OR
  - ~~(2)~~ Patient meets BOTH of the following [(1) and (2)]:
    - **(1)** Patient is not a candidate for surgery; AND
    - **(2)** According to the prescriber, the patient is not a candidate for radiation therapy.

E) Patient is Currently Receiving Odomzo. Approve.

Other Uses with Supportive Evidence

6. **Basal Cell Carcinoma, Metastatic.** Approve for 1 year if the patient meets both of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Disease is limited to nodal metastases.
   Note: This includes primary or recurrent nodal metastases. A patient with distant metastasis does not meet this requirement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Odomzo is not recommended in the following situations:

14. **Basal Cell Carcinoma (Locally Advanced or Metastatic), in a Patient with Disease Progression While on Erivedge (vismodegib capsules).** Note: This does not apply to a patient already started on Odomzo. Refer to criteria for Basal Cell Carcinoma, Locally Advanced for a Patient Currently Receiving Odomzo. Results from an open-label study (n = 9) showed resistance to Odomzo in patients with advanced basal cell carcinoma who had progressed while taking Erivedge.[6] There are no data to support the use of Odomzo in patients who have experienced disease progression on Erivedge. Previous use of a hedgehog inhibitor was not allowed in the pivotal study for Odomzo.[3] Patients who develop resistance to one of the hedgehog pathway inhibitors are not expected to respond to another hedgehog pathway inhibitor.

15. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

25. Odomzo® capsules [prescribing information]. East Hanover, NJ: Novartis; May 2019.
26. The NCCN Basal Cell Skin Cancers Clinical Practice Guidelines in Oncology (version 2.2022 – March 24, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 13, 2022.
27. Migden MR, Guminski A, Gutzmer R, et al. Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): a multicentre, randomised, double-blind phase 2 trial. *Lancet Oncol.* 2015;16(6):716-728.
28. Erivedge® capsules [prescribing information]. South San Francisco, CA: Genentech/Roche; July 2020.
29. Danial C, Sarin KY, Oro AE, Chang AL. An investigator-initiated open-label trial of sonidegib in advanced basal cell carcinoma patients resistant to vismodegib. *Clin Cancer Res.* 2016;22(6):1325-1329.
30. Dummer R, Guminski A, Gutzmer R, et al. The 12-month analysis from Basal Cell Carcinoma Outcomes with LDE225 Treatment (BOLT): A Phase II, randomized, double-blind study of sonidegib in patients with advanced basal cell carcinoma. *J Am Acad Dermatol.* 2016;75(1):113-125.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Ogsiveo Prior Authorization Policy
- Ogsiveo™ (nirogacestat tablets – SpringWorks Therapeutics)

REVIEW DATE: 11/29/2023

OVERVIEW

Ogsiveo, a gamma secretase inhibitor, is indicated for **progressing desmoid tumors** that require systemic treatment in adults.[1]

Disease Overview

Desmoid tumors, or aggressive fibromatosis, are rare soft-tissue tumors.[2] These types of tumors are locally aggressive and invasive, leading to morbidity, but rarely mortality. Desmoid tumors are not metastatic tumors. The enlarged size of some of the tumors can lead to compression of vital structures, resulting in severe pain, functional impairment, nerve damage, and bowel obstruction or perforation. Pain is associated with disease progression and can lead to opioid dependence or suboptimal pain management due to the concern for opioid dependence. Surgery used to be the mainstay of treatment; however, due to high morbidity and postsurgical recurrence rates of up to 50% to 88%, it is used less frequently. Other treatments include cytotoxic chemotherapy, tyrosine kinase inhibitors, local ablation, or radiation therapy.

Clinical Efficacy

The efficacy of Ogsiveo was assessed in a Phase III, double-blind, randomized, placebo-controlled trial in adults with progressing desmoid tumors not amenable to surgery.[1,3] Eligible patients (n = 142) were ≥ 18 years of age with a histologically confirmed diagnosis of progressing desmoid tumors, defined as ≥ 20% progression (according to Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1) within 12 months before screening. Patients were randomized to receive Ogsiveo 150 mg or placebo orally twice daily until disease progression or unacceptable toxicity. Patients treated with Ogsiveo had a significant progression-free survival benefit over placebo. In the Ogsiveo group, 17% of patients had a progression event compared with 51% of patients in the placebo group (hazard ratio 0.29; 95% confidence interval: 0.15, 0.55; $P < 0.001$). The objective response rate was also significantly better in the Ogsiveo group compared with placebo: 41% vs. 8%, respectively ($P < 0.001$).

Guidelines

Ogsiveo is not addressed in the National Comprehensive Cancer Network (NCCN) soft tissue sarcoma guidelines (version 2.2023 – April 25, 2023). Guidelines recommend the following therapies as "preferred" regimens for desmoid tumors (aggressive fibromatosis):[4] sorafenib (category 1), methotrexate and vinorelbine, methotrexate and vinblastine, imatinib, pazopanib, doxorubicin ± dacarbazine, and Doxil® (liposomal doxorubicin for intravenous injection) [except for sorafenib, all other agents listed are category 2A recommendation]. Sulindac or other nonsteroidal anti-inflammatory drugs, including celecoxib are recommended for pain under "useful in certain circumstances" (category 2A).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ogsiveo. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ogsiveo is recommended in those who meet the following criteria:

FDA-Approved Indication

3. **Desmoid Tumors (Aggressive Fibromatosis).** Approve for 1 year if the patient meets the following (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** According to the prescriber, the patient has progressing desmoid tumors; AND
     Note: Progressing desmoid tumors are defined as ≥ 20% progression within 12 months.
   - **C)** The desmoid tumors are not amenable to surgery; AND
   - **D)** According to the prescriber, the patient requires systemic treatment.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ogsiveo is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Ogsiveo™ tablets [prescribing information]. Stamford, CT: SpringWorks Therapeutics; November 2023.
2. Gounder M, Ratan R, Alcindor T, et al. Nirogacestat, a γ-secretase inhibitor for desmoid tumors. *N Engl J Med.* 2023;388:898-912.
3. Gounder M, Ratan R, Alcindor T, et al. Nirogacestat, a γ-secretase inhibitor for desmoid tumors. *N Engl J Med.* 2023;388:898-912.
4. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed November 28, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Ojjaara Prior Authorization Policy
- Ojjaara™ (momelotinib tablets – GlaxoSmithKline)

REVIEW DATE: 09/20/2023; selected revision 11/08/2023

OVERVIEW

Ojjaara, a Janus Kinase (JAK1/JAK2) inhibitor and activin A receptor type 1 (ACVR1) inhibitor (also known as activin receptor like kinase 2 [ALK2]), is indicated for the treatment of intermediate or high-risk myelofibrosis (MF), including primary MF or secondary MF (post-polycythemia vera and post-essential thrombocythemia), in adults with anemia.[1]

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines for myeloproliferative neoplasms (version 3.2023 – October 25, 2023) have recommendations for MF.[2] Ojjaara is a "preferred" regimen for the management of MF-associated anemia in patients with serum erythropoietin ≥ 500 mU/mL (category 2A). For patients with higher-risk MF with platelet count ≥ 50 x 10^9/L who are not transplant candidates, Jakafi® (ruxolitinib tablets) [category 1], Inrebic® (fedratinib capsules) [category 1], Ojjaara (category 2A), or Vonjo ® (pacritinib capsules) [category 2B] are recommended; for patients who had no response or loss of response to initial therapy, Jakafi, Inrebic, Ojjaara (all category 2A), or Vonjo (category 2B) are recommended if they were not previously used. For patients with higher-risk MF with platelet count < 50 x 10^9/L who are not candidates for transplant, NCCN recommends Vonjo as a "preferred" therapy (category 1) and Ojjaara as "other recommended regimens" (category 2B). For lower-risk symptomatic patients with MF, Jakafi (category 2A) and Ojjaara (category 2B) are considered "useful in certain circumstances" for first-line therapy; for patients who had no response or loss of response to first-line therapy, Jakafi (category 2A), Ojjaara (category 2B), and Vonjo [for patients with platelets < 50 x 10^9/L] {category 2A} can be used.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ojjaara. All approvals are provided for the duration noted below.

Automation: none

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ojjaara is recommended in those who meet the following criteria:

FDA-Approved Indication

7. Myelofibrosis. Approve for 1 year if the patient meets the following (A, B, and C):
Note: Examples of myelofibrosis include primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis.
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has intermediate-risk or high-risk disease; AND
- **C)** Patient meets one of the following (i or ii):
  - **i.** Patient has anemia and meets both of the following (a and b):

a) Patient has hemoglobin < 10 g/dL AND
b) Patient has serum erythropoietin level ≥ 500 mU/mL; OR

ii. Patient has platelet count ≥ 50 X 10^9/L.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ojjaara is not recommended in the following situations:

16. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

31. Ojjaara™ tablets [prescribing information]. Durham, NC: GlaxoSmithKline; September 2023.
32. The NCCN Myeloproliferative Neoplasms Clinical Practice Guidelines in Oncology (version 3.2023 – October 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 31, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Onureg Prior Authorization Policy
- Onureg® (azacitidine tablets – Celgene)

REVIEW DATE: 09/13/2023

OVERVIEW

Onureg, a nucleoside metabolic inhibitor, is indicated for the continued treatment of **acute myeloid leukemia** (AML) in adults who achieve first complete remission or complete remission with incomplete blood count recovery following intensive induction chemotherapy and are unable to complete intensive curative therapy.[1]

Guidelines

The National Comprehensive Cancer Network AML guidelines (version 4.2023 – July 11, 2023) recommend Onureg for the post-remission maintenance treatment of AML in patients with intermediate- or adverse-risk disease, who completed no consolidation, some consolidation, or are recommended to receive a course of consolidation; and with no allogeneic stem cell transplantation planned (category 1).[2,3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Onureg. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Onureg is recommended in those who meet the following criteria:

FDA-Approved Indication

4. Acute Myeloid Leukemia. Approve for 1 year if the patient meets the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The medication is used for post-remission maintenance therapy; AND
- **C)** Patient has intermediate- or poor-risk cytogenetics; AND
  Note: Examples of intermediate- and poor-risk cytogenetics include the following genetic alterations: wild-type *NPM1* without *FLT3-ITD* or with *FLT3-ITD^{low}*, *MLLT3-KMT2A*, *DEK-NUP214*, and *KMT2A* rearranged.
- **D)** According to the prescriber, allogeneic hematopoietic stem cell transplant is not planned.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Onureg is not recommended in the following situations:

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

5. Onureg® tablets [prescribing information]. Summit, NJ: Celgene; May 2021.
6. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 4.2023 – July 11, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed September 8, 2023.
7. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed September 8, 2023. Search term: Onureg.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Orgovyx Prior Authorization Policy
- Orgovyx® (relugolix tablets – Myovant Sciences/Pfizer)

REVIEW DATE: 01/25/2023

OVERVIEW
Orgovyx, a gonadotropin-releasing hormone (GnRH) receptor antagonist, is indicated for the treatment of **advanced prostate cancer** in adults.[1]

Guidelines
The National Comprehensive Cancer Network (NCCN) prostate cancer guidelines (version 1.2023 – September 16, 2022) recommend the use of androgen deprivation therapy (ADT) for various stages of prostate cancer. Orgovyx is listed as an option for ADT for clinically localized (regional node 0 [N0], distant metastases 0 [M0]), regional (N1, M0) disease, or M0 or M1 castration-naïve disease (category 2A).[2,3] The guidelines note that Orgovyx has not been adequately studied in combination with potent androgen receptor inhibitors, such as abiraterone acetate, Xtandi® (enzalutamide capsules and tablets), Erleada® (apalutamide tablets), Nubeqa® (darolutamide tablets), nor has it be studied in combination with docetaxel or cabazitaxel chemotherapy.[2]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Orgovyx. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Orgovyx is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Prostate Cancer.** Approve for 1 year if the patient is ≥ 18 years of age.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Orgovyx is not recommended in the following situations:

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

8. Orgovyx® tablets [prescribing information]. Brisbane, CA: Myovant Sciences/Pfizer; September 2022.
9. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – September 16, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed January 24, 2023.

10. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 24, 2023. Search term: relugolix.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Orserdu Prior Authorization Policy
- Orserdu™ (elacestrant tablets – Stemline/Menarini)

REVIEW DATE: 02/08/2023; selected revision 02/15/2023

OVERVIEW

Orserdu, an estrogen receptor antagonist, is indicated for the treatment of postmenopausal women or adult men with estrogen receptor-positive (ER+), human epidermal growth factor receptor 2 (HER2)-negative, estrogen receptor 1 gene (*ESR1)*-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.[1]

Guidelines

National Comprehensive Cancer Network (NCCN) breast cancer guidelines (version 2.2023 – February 7, 2023) recommend Orserdu for ER+, HER2-negative, *ESR1*-mutated recurrent, unresectable or metastatic breast cancer after progression on one or two prior lines of endocrine therapy, including one line containing a cyclin-dependent kinase (CDK)4/6 inhibitor as other recommended regimens (category 2A). Preferred regimens for second-and subsequent-line therapy include fulvestrant + CDK4/6 inhibitor (Kisqali® [ribociclib tablets], Ibrance® [palbociclib tablets or capsules], or Verzenio® [abemaciclib tablets]) if CDK4/6 inhibitor was not previously used (category 1), Piqray® (alpelisib tablets) + fulvestrant for phosphatidylinositol-3-kinase (*PIK3CA*)-mutated tumors (category 1), and everolimus + endocrine therapy (exemestane, fulvestrant, or tamoxifen) [category 2A]. Other recommended regimens for subsequent-line therapy include selective ER down-regulator (fulvestrant, category 1) + non-steroidal aromatase inhibitor (anastrozole, letrozole) [category 1]; single agent therapy with fulvestrant, anastrozole, letrozole, tamoxifen, or exemestane (category 2A). There are also other agents recommended that are useful in certain circumstances for subsequent-line therapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Orserdu. All approvals are provided for the duration noted below. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: a woman is defined as an individual with the biological traits of a woman, regardless of the individual's gender identity or gender expression; a man is defined as an individual with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Orserdu is recommended in those who meet the following criteria:

FDA-Approved Indication

5. **Breast Cancer in Postmenopausal Women or Men***. Approve for 1 year if the patient meets the following criteria (A, B, C, D, E, and F):
   - **F)** Patient is ≥ 18 years of age; AND
   - **G)** Patient has recurrent or metastatic disease; AND

H) Patient has estrogen receptor positive (ER+) disease; AND
I) Patient has human epidermal growth factor receptor 2 (HER2)-negative disease; AND
J) Patient has estrogen receptor 1 gene (*ESR1)*-mutated disease; AND
K) Patient has tried at least one endocrine therapy.
Note: Examples of endocrine therapy include fulvestrant, anastrozole, exemestane, letrozole, and tamoxifen.

***** Refer to the Policy Statement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Orserdu is not recommended in the following situations:

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

11. Orserdu™ tablets [prescribing information]. New York, NY: Stemline Therapeutics/Menarini Group; January 2023.
12. Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: results from the randomized phase III EMERALD trial. *J Clin Oncol*. 2022; 40:3246-3256.
13. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – February 7, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 7, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Pemazyre Prior Authorization Policy
- Pemazyre® (pemigatinib tablets – Incyte)

REVIEW DATE: 05/10/2023

OVERVIEW

Pemazyre, a kinase inhibitor, is indicated in adults for the following uses:[1]
- Previously treated, unresectable locally advanced or metastatic **cholangiocarcinoma** with a fibroblast growth factor receptor 2 (*FGFR2*) fusion or other rearrangement as detected by an FDA-approved test.
- Relapsed or refractory **myeloid/lymphoid neoplasms** with fibroblast growth factor receptor 1 (*FGFR1*) rearrangement.

Guidelines

Pemazyre is addressed in National Comprehensive Cancer Network (NCCN) guidelines:[2]
- **Biliary tract cancers**: Guidelines (version 1.2023 – March 10, 2023) recommend Pemazyre for disease progression on or following systemic treatment for patients with unresectable or metastatic cholangiocarcinoma with *FGFR2* fusion or rearrangement, as a single agent (category 2A).[3]
- **Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes**: Guidelines (version 2.2022 – October 18, 2022) recommend Pemazyre for the treatment of myeloid/lymphoid neoplasms with eosinophilia and *FGFR1* rearrangement in chronic phase or blast phase (category 2A).[2,4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Pemazyre. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Pemazyre is recommended in those who meet one of the following criteria:

FDA-Approved Indications

6. Cholangiocarcinoma. Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has unresectable locally advanced or metastatic disease; AND
- **C)** Tumor has fibroblast growth factor receptor 2 (*FGFR2*) fusion or other rearrangement, as detected by an approved test; AND
- **D)** Patient has been previously treated with at least one systemic regimen.
  Note: Examples of systemic regimens are gemcitabine + cisplatin, 5-fluorouracil + oxaliplatin or cisplatin, capecitabine + cisplatin or oxaliplatin, gemcitabine + Abraxane (albumin-bound paclitaxel) or capecitabine or oxaliplatin, gemcitabine + Abraxane + cisplatin, FOLFOX (5-

fluorouracil, leucovorin, and oxaliplatin), FOLFIRI (5-fluorouracil, leucovorin, irinotecan), Stivarga (regorafenib tablets).

7. **Myeloid/Lymphoid Neoplasms.** Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has eosinophilia; AND
   - **C)** The cancer has fibroblast growth factor receptor 1 (*FGFR1*) rearrangement, as detected by an approved test; AND
   - **D)** The cancer is in chronic phase or blast phase.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Pemazyre is not recommended in the following situations:

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

9. Pemazyre® tablets [prescribing information]. Wilmington, DE: Incyte; August 2022.
10. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 4, 2023. Search term: pemigatinib.
11. The NCCN Biliary Tract Cancers Clinical Practice Guidelines in Oncology (version 1.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 5, 2023.
12. The NCCN Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes Clinical Practice Guidelines in Oncology (version 2.2022 – October 18, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 4, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Piqray Prior Authorization Policy
- Piqray® (alpelisib tablets – Novartis)

REVIEW DATE: 07/12/2023

OVERVIEW

Piqray, a kinase inhibitor, is indicated in combination with fulvestrant injection for the treatment of postmenopausal women and men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, phosphatidylinositol-3-kinase (*PIK3CA*)-mutated, **advanced or metastatic breast cancer** as detected by an FDA-approved test following progression on or after an endocrine-based regimen.[1]

Patients treated with Piqray should have one or more *PIK3CA* mutations in tumor tissue or plasma specimens. If no mutation is detected in a plasma specimen, tumor tissue should be tested. Information on FDA-approved tests for the detection of *PIK3CA* mutations in breast cancer is available on the FDA website.[2]

Guidelines

Piqray is discussed in the guidelines from National Comprehensive Cancer Network (NCCN).[3,4] NCCN breast cancer guidelines (version 4.2023 – March 23, 2023) recommend Piqray, in combination with fulvestrant, as a preferred second-line regimen or subsequent-line therapy for *PIK3CA*-activating mutation in postmenopausal or premenopausal patients (receiving ovarian ablation or suppression, if premenopausal) with HR+/HER2-negative, recurrent unresectable (local or regional) or Stage IV disease (category 1).[3] It is noted that the safety of Piqray in patients with type 1 or uncontrolled type 2 diabetes has not been established. Preferred first-line regimens for HR+/HER2-negative disease include the following: aromatase inhibitor (i.e., letrozole, anastrozole, exemestane) + CDK4/6 inhibitor (i.e., Ibrance® [palbociclib capsules], Kisqali® [ribociclib tablets], Verzenio® [abemaciclib tablets]) or fulvestrant + CDK4/6 inhibitor. Of note, men with breast cancer are treated similarly to postmenopausal women.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Piqray. All approvals are provided for the duration noted below. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: a woman is defined as an individual with the biological traits of a woman, regardless of the individual's gender identity or gender expression; men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Piqray is recommended in those who meet the following criteria:

FDA-Approved Indication

8. Breast Cancer. Approve for 1 year if the patient meets the following (A, B, C, D, E, F, and G):

A) Patient is ≥ 18 years of age; AND

B) Patient meets one of the following (i or ii):

i. Patient is a postmenopausal female* or a male*; OR

ii. Patient is pre/perimenopausal and meets one of the following (a or b):

a) Patient is receiving ovarian suppression with a gonadotropin-releasing hormone (GnRH) agonist; OR

Note: Examples of a GnRH agonist include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous injection).

b) Patient has had surgical bilateral oophorectomy or ovarian irradiation; AND

C) Patient has advanced or metastatic hormone receptor (HR)-positive disease; AND

D) Patient has human epidermal growth factor receptor 2 (HER2)-negative disease; AND

E) Patient has *PIK3CA*-mutated breast cancer as detected by an approved test; AND

F) Patient has progressed on or after at least one prior endocrine-based regimen; AND

Note: Examples of an endocrine-based regimen contains one of the following products: anastrozole, letrozole, exemestane, tamoxifen, toremifene, or fulvestrant.

G) Piqray will be used in combination with fulvestrant injection.

* Refer to Policy Statement

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Piqray is not recommended in the following situations:

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

13. Piqray® tablets [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; November 2022.
14. Food and Drug Administration. Lists of cleared or approved companion diagnostic devices (in vitro and imaging tools). Available at: https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools. Accessed on July 6, 2023.
15. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – March 23, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 6, 2023.
16. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 6, 2023. Search term: alpelisib.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Pomalyst Prior Authorization Policy
- Pomalyst® (pomalidomide capsules – Celgene)

REVIEW DATE: 05/10/2023

OVERVIEW

Pomalyst, a thalidomide analog, is indicated for the following uses:[1]

- **Kaposi sarcoma,** adults with Acquired Immune Deficiency Syndrome (AIDS)-related Kaposi sarcoma after failure of highly active antiretroviral therapy (HAART) or in adults with Kaposi sarcoma who are human immunodeficiency virus (HIV)-negative.
- **Multiple myeloma**, in combination with dexamethasone, in adults who have received at least two prior therapies including lenalidomide capsules and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Guidelines

Pomalyst is addressed in guidelines from National Comprehensive Cancer Network (NCCN):[3,5-7]

- **Central Nervous System (CNS) Cancers:** The NCCN has guidelines regarding CNS cancers (version 1.2023 – March 24, 2023).[5] Pomalyst is listed as a recommended regimen for patients with relapsed or refractory disease for primary CNS lymphoma.
- **Kaposi Sarcoma:** The NCCN has guidelines regarding Kaposi sarcoma (version 1.2023 – December 20, 2022).[3] Pomalyst is cited as the preferred subsequent system therapy option given alone (in patients without HIV) or with antiretroviral therapy for patients with HIV for relapsed/refractory advanced cutaneous, oral, visceral, or nodal disease that has not progressed on or not responded for first-line systemic therapy and progressed on alternate first-line systemic therapy. First-line systemic therapy options include liposomal doxorubicin (preferred) and paclitaxel.
- **Multiple Myeloma:** The NCCN guidelines for multiple myeloma (version 3.2023 – December 8, 2022) include Pomalyst.[6] Pomalyst is recommended in various clinical regimens after use of previous therapies in varying scenarios and with different agents among patients with multiple myeloma that has been previously treated (including as a category 1 and category 2A recommendation). It can be used as a monotherapy for patients who are steroid intolerant. Pomalyst is also indicated for treatment in combination with dexamethasone for the management of POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome as induction therapy for transplant eligible patients and for transplant ineligible patients.
- **Systemic Light Chain Amyloidosis:** The NCCN has guidelines for systemic light chain amyloidosis (version 2.2023 – November 28, 2022).[7] The guidelines list Pomalyst plus dexamethasone as one of several treatment options for patients with previously treated disease (category 2A). Many other regimens are cited as primary therapy for transplant candidates and non-transplant candidates.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Pomalyst. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Pomalyst is recommended in those who meet one of the following criteria:

FDA-Approved Indications

8. **Kaposi Sarcoma.** Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets one of the following (i or ii):
     - **i.** Patient is Human Immunodeficiency Virus (HIV)-negative; OR
     - **ii.** Patient meets both of the following (a and b):
       - **a)** Patient is HIV-positive; AND
       - **b)** Patient continues to receive highly active antiretroviral therapy.

9. **Multiple Myeloma.** Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has received at least one other lenalidomide containing regimen.

Other Uses with Supportive Evidence

10. **Central Nervous System Lymphoma.** Approve for 1 year if the patient has relapsed or refractory disease.

11. **POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) Syndrome.** Approve for 1 year if the patient meets and following (A and B):
    - **C)** Patient is ≥ 18 years of age; AND
    - **D)** Use of Pomalyst is in combination with dexamethasone.

12. **Systemic Light Chain Amyloidosis.** Approve for 1 year if the patient meets the following (A, B, and C):
    - **A)** Patient is ≥ 18 years of age; AND
    - **B)** Use of Pomalyst is in combination with dexamethasone; AND
    - **C)** Patient has tried at least one other regimen.
      Note: Examples of regimens include lenalidomide plus dexamethasone; bortezomib, lenalidomide, cyclophosphamide, and dexamethasone; bortezomib with or without dexamethasone; bortezomib, lenalidomide, and dexamethasone; melphalan and dexamethasone; bortezomib, cyclophosphamide, and dexamethasone; and Darzalex (daratumumab intravenous infusion)/Darzalex Faspro (daratumumab and hyaluronidase-fihj subcutaneous injection).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Pomalyst is not recommended in the following situations:

17. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

7. Pomalyst® capsules [prescribing information]. Summit, NJ: Celgene; March 2023.
8. The NCCN Kaposi Sarcoma Clinical Practice Guidelines in Oncology (version 1.2023 – December 20, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 8, 2023.
9. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 1.2023 – March 24, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 8, 2023.
10. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 3.2023 – December 8, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 8, 2023.
11. The NCCN Systemic Light Chain Amyloidosis Clinical Practice Guidelines in Oncology (version 2.2023 – November 28, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 8, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Qinlock Prior Authorization Policy
- Qinlock® (ripretinib tablets – Deciphera Pharmaceuticals)

REVIEW DATE: 04/19/2023

OVERVIEW

Qinlock, a kinase inhibitor, is indicated for the treatment of advanced **gastrointestinal stromal tumor** in adults who have received prior treatment with three or more kinase inhibitors, including imatinib.[1]

Guidelines

Qinlock is discussed in the guidelines from the National Comprehensive Cancer Network (NCCN):

- **Gastrointestinal Stromal Tumor**: NCCN guidelines (version 1.2023 – March 13, 2023) recommend Qinlock for unresectable or metastatic disease in the following situations: Qinlock 150 mg daily for second-line therapy for patients who are intolerant of second-line sunitinib as a "Preferred Regimen" (category 2A); Qinlock 150 mg daily as fourth-line therapy after therapy with imatinib, sunitinib, and Stivarga® (regorafenib tablets) as a "Preferred Regimen" (category 1); Qinlock dose escalation to 150 mg twice daily if patient has previously progressed on Qinlock 150 mg daily as additional options after progression on approved therapies as "useful in certain circumstances"(category 2A); and Qinlock 150 mg daily or Qinlock 150 mg twice daily (if previously progressed with 150 mg daily) after progression with Ayvakit® (avapritinib tablets) and Sprycel® (dasatinib tablets).[2,3]
- **Melanoma: Cutaneous**: NCCN guidelines (version 2.2023 – March 10, 2023) recommend Qinlock as "useful in certain circumstances" for metastatic or unresectable disease with an activating *KIT* mutation as second-line or subsequent therapy for disease progression, intolerance, and/or projected risk of progression with *BRAF*-targeted therapy.[2,4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Qinlock. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Qinlock is recommended in those who meet the following criteria:

FDA-Approved Indication

9. Gastrointestinal Stromal Tumor. Approve for 1 year if the patient meets the following criteria (A, B and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has tried imatinib or Ayvakit (avapritinib tablets); AND
- **C)** Patient meets one of the following criteria (i, ii, or iii):
  - **i.** Patient has tried sunitinib and Stivarga (regorafenib tablets); OR
  - **ii.** Patient has tried Sprycel (dasatinib tablets); OR

iii. Patient is intolerant of sunitinib.

Other Uses with Supportive Evidence

10. Melanoma, Cutaneous. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has metastatic or unresectable disease; AND
- **C)** Patient has an activating *KIT* mutation; AND
- **D)** Patient has tried at least one systemic regimen.

  Note: Examples of a systemic regimen include: Opdivo (nivolumab intravenous infusion) + Yervoy (ipilimumab intravenous infusion), Opdivo + Opdualag (nivolumab/relatlimab-rmbw intravenous infusion), Keytruda (pembrolizumab intravenous infusion), Opdivo, Tafinlar (dabrafenib capsules) + Mekinist (trametinib tablets), Zelboraf (vemurafenib tablets) + Cotellic (cobimetinib tablets), Braftovi (encorafenib capsules) + Mektovi (binimetinib tablets).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Qinlock is not recommended in the following situations:

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

17. Qinlock™ tablets [prescribing information]. Waltham, MA: Deciphera Pharmaceuticals; December 2022.
18. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on April 10, 2023.
19. The NCCN Gastrointestinal Stromal Tumor (GIST) Clinical Practice Guidelines in Oncology (version 1.2023 – March 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on April 17, 2023.
20. The NCCN Melanoma: Cutaneous Clinical Practice Guidelines in Oncology (version 2.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on April 10, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Retevmo Prior Authorization Policy
- Retevmo® (selpercatinib capsules – Eli Lilly)

REVIEW DATE: 06/14/2023

OVERVIEW

Retevmo, a kinase inhibitor, is indicated for the following uses:[1]

- **Non-small cell lung cancer**, locally advanced or metastatic with a rearranged during transfection (*RET*) gene fusion, as detected by an FDA-approved test in adults.
- **Solid tumors,** locally advanced or metastatic solid tumors with a *RET* gene fusion in patients who have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.
- **Thyroid cancer**, advanced or metastatic *RET*-mutant medullary, in patients ≥ 12 years of age who require systemic therapy.
- **Thyroid cancer**, advanced or metastatic *RET* fusion-positive, in patients ≥ 12 years of age who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate), as detected by an FDA-approved test.

All of the indications above except non-small cell lung cancer were accelerated approvals based on overall response rate and duration of response. Continued approval of these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

Guidelines

Retevmo is addressed in the National Comprehensive Cancer Network (NCCN) compendium for an variety of solid tumors.[2] Retevmo is addressed in NCCN guidelines:

- **Histiocytic Neoplasms:** NCCN guidelines (version 1.2022 – May 20, 2022) recommend Retevmo as an agent that may be useful as the first- or subsequent-line treatment for the following types of histiocytic neoplasm with *RET* fusion: Langerhans cell histiocytosis, Erdheim-Chester disease, and Rosai-Dorfman disease (category 2A).[3]
- **Non-Small Cell Lung Cancer:** NCCN guidelines (version 3.2023 – April 13, 2023) recommend Retevmo as a preferred option for first-line and subsequent treatment of patients with *RET* rearrangement-positive recurrent, advanced, or metastatic non-small cell lung cancer (category 2A).[2,4]
- **Thyroid Carcinoma:** NCCN guidelines (version 2.2023 – May 18, 2023) recommend Retevmo and Gavreto® (pralsetinib capsules) as "preferred regimens" for the treatment of *RET* mutation-positive recurrent or persistent locoregional or metastatic medullary carcinoma (category 2A).[5] Retevmo is also recommended for the treatment of locally recurrent, advanced, and/or metastatic *RET*-fusion positive thyroid carcinoma that is not amenable to radioactive iodine therapy as "useful in certain circumstances" (category 2A). Additionally NCCN recommends Retevmo for *RET*-fusion positive anaplastic thyroid carcinoma for locoregional disease and metastatic disease (category 2A).[5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Retevmo. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Retevmo is recommended in those who meet one of the following criteria:

FDA-Approved Indications

11. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has recurrent, advanced, or metastatic disease; AND
- **C)** The tumor is rearranged during transfection (*RET)* fusion-positive.

12. Thyroid Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 12 years of age; AND
- **B)** Patient has rearranged during transfection (*RET)* fusion-positive or *RET* mutation-positive disease; AND
- **C)** Patient meets ONE of the following criteria (i or ii):
  - **i.** Patient has anaplastic thyroid cancer; OR
  - **ii.** The disease requires treatment with systemic therapy and patient meets ONE of the following criteria (a or b):
    - **a)** The patient has medullary thyroid cancer; OR
    - **b)** The disease is radioactive iodine-refractory.

13. Solid Tumors. Approve for 1 year if the patient meets the following criteria (A, B, and C):
Note: Examples of solid tumors include breast cancer, cervical cancer, cholangiocarcinoma, colorectal cancer, esophageal cancer, gastric cancer, ovarian cancer, pancreatic adenocarcinoma, salivary gland tumors, soft tissue sarcoma, small bowel adenocarcinoma, and unknown primary cancer.
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has recurrent, advanced, or metastatic disease; AND
- **C)** The tumor is rearranged during transfection (*RET)* fusion-positive.

Other Uses with Supportive Evidence

14. Histiocytic Neoplasm. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **E)** Patient is ≥ 18 years of age; AND
- **F)** Patient meets one of the following (i, ii, or iii):
  - **i.** Patient has Langerhans cell histiocytosis; OR
  - **ii.** Patient has Erdheim-Chester disease; OR
  - **iii.** Patient has Rosai-Dorfman disease; AND
- **G)** Patient has a rearranged during transfection (*RET)* fusion.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Retevmo is not recommended in the following situations:

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

21. Retevmo® capsules [prescribing information]. Indianapolis, IN: Eli Lilly and Company; September 2022.
22. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 7, 2023. Search term: selpercatinib.
23. The NCCN Histiocytic Neoplasms Clinical Practice Guidelines in Oncology (version 1.2022 – May 20, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 7, 2023.
24. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – April 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 7, 2023.
25. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (version 2.2023 – May 18, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 7, 2023

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Rezlidhia Prior Authorization Policy
- Rezlidhia™ (olutasidenib capsules – Rigel)

REVIEW DATE: 12/13/2023

OVERVIEW
Rezlidhia, an isocitrate dehydrogenase-1 (*IDH1*) inhibitor, is indicated for the treatment of relapsed or refractory **acute myeloid leukemia** with a susceptible *IDH1* mutation as detected by an FDA-approved test in adults.

Guidelines
The National Comprehensive Cancer Network (NCCN) acute myeloid leukemia guidelines (version 6.2023 – October 24, 2023) recommend Rezlidhia or Tibsovo® (ivosidenib tablets) for patients with relapsed or refractory AML with an *IDH1* mutation (both category 2A).

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Rezlidhia. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Rezlidhia is recommended in those who meet the following criteria:

FDA-Approved Indication

13. Acute Myeloid Leukemia. Approve for 1 year if the patient meets the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has relapsed or refractory disease; AND
- **C)** Patient has isocitrate dehydrogenase-1 (*IDH1*) mutation positive disease as detected by an approved test.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Rezlidhia is not recommended in the following situations:

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

14. Rezlidhia™ capsules [prescribing information]. San Francisco, CA: Rigel; December 2022.
15. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 6.2023 – October 24, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 1, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Rozlytrek Prior Authorization Policy
- Rozlytrek® (entrectinib capsules and oral pellets – Genentech)

REVIEW DATE: 09/27/2023; selected revision 11/22/2023

OVERVIEW

Rozlytrek, a kinase inhibitor, is indicated for the following uses:[1]

- **Non-small cell lung cancer (NSCLC)**, with *ROS1*-positive metastatic disease, as detected by an FDA-approved test, in adults.
- **Solid tumors**, in adult and pediatric patients ≥ 1 month of age that:
  - Have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion, as detected by an FDA-approved test without a known acquired resistance mutation; AND
  - Are metastatic or surgical resection of the tumor is likely to result in severe morbidity; AND
  - Have either progressed following treatment or there are no satisfactory alternative therapies.

Guidelines

Rozlytrek is addressed in guidelines by the National Comprehensive Cancer Network (NCCN):[2,3]

- **NSCLC.** Guidelines (version 3.2023 – April 13, 2023) recommend Rozlytrek as a preferred first-line treatment option for patients with *ROS1* rearrangement-positive NSCLC (category 2A).[2] Rozlytrek is also recommended as a preferred first-line treatment option for patients with *NTRK* gene fusion-positive NSCLC (category 2A).
- **Solid tumors.** The NCCN Drugs and Biologics Compendium notes the use of Rozlytrek for *NTRK* gene fusion-positive tumors associated with the following cancers: ampullary adenocarcinoma, breast cancer, central nervous system cancers (e.g., glioma, glioblastoma, brain metastases), cervical cancer, colon cancer, esophageal and esophagogastric junction cancers, gastric cancer, gastrointestinal stromal tumors, head and neck cancers (e.g., salivary gland tumors), hepatobiliary cancers, histiocytic neoplasms, melanoma (cutaneous), non-small cell lung cancer, ovarian cancer/fallopian tube cancer/primary peritoneal cancer, pancreatic cancer, rectal cancer, small bowel adenocarcinoma, soft tissue sarcomas, thyroid carcinoma, uterine neoplasms, and vulvar cancer.[3] Rozlytrek is a category 2A recommendation for most of these cancers. Rozlytrek is recommended for use as a first-line and/or second-line treatment option for these cancers.
- **Pediatric Central Nervous System Cancers.** Guidelines (version 2.2023 – October 31, 2022) recommend Rozlytrek as adjuvant therapy and for recurrent or progressive disease (category 2A for both), for *TRK* fusion-positive pediatric diffuse high-grade gliomas.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Rozlytrek. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rozlytrek is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Non-Small Cell Lung Cancer.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   Note: If the patient has non-small cell lung cancer with neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion, see **Solid Tumors** indication.
   A) Patient is ≥ 18 years of age; AND
   B) Patient has metastatic disease; AND
   C) Patient has *ROS1*-positive disease; AND
   D) The mutation was detected by an approved test.

2. **Solid Tumors.** Approve for 1 year if the patient meets the following (A, B, and C):
   Note: Examples of solid tumors include breast cancer, colorectal cancer, head/neck cancer, hepatocellular carcinoma, biliary cancer, histiocytic neoplasm, non-small cell lung cancer (*NTRK* gene fusion-positive), ovarian cancer, pancreatic cancer, salivary gland tumors, sarcoma, thyroid cancer, adult glioma.
   A) Patient is ≥ 1 month of age; AND
   B) The tumor is positive for neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion; AND
   C) Patient meets one of the following (i or ii):
      i. The tumor is metastatic; OR
      ii. Surgical resection of tumor will likely result in severe morbidity.

Other Uses with Supportive Evidence

3. **Pediatric Diffuse High-Grade Gliomas.** Approve for 1 year if the patient meets the following (A, B, and C):
   A) Patient is < 18 years of age; AND
   B) The tumor is positive for neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion; AND
   C) Patient meets one of the following (i or ii):
      i. The medication is used as adjuvant therapy; OR
      ii. The medication is used for recurrent or progressive disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rozlytrek is not recommended in the following situations:

18. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

33. Rozlytrek® capsules and oral pellets [prescribing information]. South San Francisco, CA: Genentech; October 2023.
34. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – April 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 25, 2023.
35. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 12, 2023. Search term: entrectinib.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Rubraca Prior Authorization Policy
- Rubraca® (rucaparib tablets – Clovis Oncology)

REVIEW DATE: 01/11/2023

OVERVIEW

Rubraca, a poly (ADP-ribose) polymerase (PARP) inhibitor, is indicated for the following uses:[1]

- **Ovarian, fallopian tube, or primary peritoneal cancer, maintenance treatment** of adults with a deleterious *BRCA* mutation (germline and/or somatic)-associated recurrent epithelial disease who are in a complete or partial response to platinum-based chemotherapy.
- **Prostate cancer**, metastatic castration-resistant (mCRPC), treatment of adults with a deleterious *BRCA* mutation (germline and/or somatic)-associated disease who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy.

Guidelines

Rubraca is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):

- **Ovarian Cancer:** NCCN guidelines (version 1.2023 – December 22, 2022) recommend single-agent Rubraca as maintenance therapy if the patient has had a complete or partial response to primary treatment in the following situations: no bevacizumab was used during primary therapy (category 2A) or bevacizumab was used during primary therapy and the patient has a germline or somatic *BRCA* mutation (category 2A).[2] In patients with platinum-sensitive disease who have completed two or more lines of platinum-based therapy and are in a partial or complete response, bevacizumab can be continued as maintenance therapy or Rubraca can be considered as maintenance therapy option if patient has a *BRCA* mutation and patient has not previously received a PARP inhibitor (category 1). Rubraca is also recommended as a preferred recurrence therapy for patients with platinum-sensitive or platinum-resistant ovarian cancer that has been treated with two or more lines of chemotherapy and have *BRCA* mutations (category 3).
- **Prostate Cancer:** NCCN guidelines (version 1.2023 – September 16, 2022) recommend Rubraca for *BRCA1* or *BRCA2* mutation (germline and/or somatic) for patients who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy in mCRPC, either as second-line or subsequent therapy (category 2A). It is listed under "useful in certain circumstances". The guidelines note that if the patient is not fit for chemotherapy, Rubraca can be considered even if taxane-based therapy has not been given.[3]
- **Uterine Neoplasms:** NCCN guidelines (version 1.2023 – December 22, 2022) state that Rubraca may be considered as a single-agent second-line therapy, useful in certain circumstances, for *BRCA2*-altered uterine leiomyosarcoma (category 2A).[4,5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Rubraca. All approvals are provided for the duration note below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rubraca is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Ovarian, Fallopian Tube, or Primary Peritoneal Cancer –Maintenance Therapy.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient is in complete or partial response after a platinum-based chemotherapy regimen; AND
     Note: Examples are carboplatin with gemcitabine, carboplatin with paclitaxel, cisplatin with gemcitabine.
   - **C)** Patient meets one of the following criteria (i or ii):
     - **i.** Patient meets both of the following criteria (a and b):
       - **a**) Patient has recurrent disease; AND
       - **b**) Patient has a *BRCA* mutation; OR
     - **ii.** Patient is in complete or partial response to first-line primary treatment.

2. **Prostate Cancer.** Approve for 1 year if the patient meets the following criteria (A, B, C, D, E, and F):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has metastatic castration resistant prostate cancer AND
   - **C)** Patient has *BRCA* mutation-positive (germline and/or somatic) disease; AND
   - **D)** Patient meets one of the following criteria (i or ii):
     - **i.** The medication is used concurrently with a gonadotropin-releasing hormone (GnRH) analog; OR
       Note: Examples are leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection),), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Vantas (histrelin acetate subcutaneous implant), Firmagon (degarelix subcutaneous injection), Orgovyx (relugolix tablets).
     - **ii.** Patient has had a bilateral orchiectomy; AND
   - **E)** Patient has been previously treated with at least one androgen receptor-directed therapy; AND
     Note: Androgen receptor-directed therapy includes abiraterone, Xtandi (enzalutamide tablets), Nubeqa (darulutamide tablets), or Erleada (apalutamide tablets).
   - **F)** Patient meets one of the following criteria (i or ii):
     - **i.** Patient has been previously treated with at least one taxane-based chemotherapy; OR
       Note: Examples are docetaxel, cabazitaxel.
     - **ii.** Patient is not a candidate or is intolerant to taxane-based chemotherapy, according to the prescriber.

Other Uses with Supportive Evidence:

3. **Ovarian, Fallopian Tube, or Primary Peritoneal Cancer – Treatment.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has a *BRCA* mutation (germline or somatic) as confirmed by an approved test; AND
   - **C)** Patient has progressed on two or more prior lines of chemotherapy.

4. **Uterine Leiomyosarcoma**. Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **D)** Patient is ≥ 18 years of age; AND
   - **E)** Patient has *BRCA2*-altered disease; AND
   - **F)** Patient has tried one systemic regimen.
     Note: Examples of a systemic regimen include one or more of the following products: dacarbazine, docetaxel, doxorubicin, epirubicin, gemcitabine, ifosfamide, vinorelbine.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rubraca is not recommended in the following situations:

19. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

29. Rubraca® tablets [prescribing information]. Boulder, CO: Clovis Oncology; December 2022
30. The NCCN Ovarian Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed January 10, 2023.
31. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – September 16, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed January 10, 2023.
32. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed January 9, 2023.
33. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 10, 2023. Search term: rucaparib.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Rydapt Prior Authorization Policy
- Rydapt® (midostaurin capsules – Novartis)

REVIEW DATE: 03/08/2023

OVERVIEW

Rydapt, a tyrosine kinase inhibitor, is indicated in adults for the following uses:[1]

- **Acute myeloid leukemia, newly diagnosed, that is FMS-like tyrosine kinase 3 (*FLT3*) mutation-positive** as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation. Limitations of use: Rydapt is not indicated as a single-agent induction therapy for treatment of patients with acute myeloid leukemia.
- **Aggressive systemic mastocytosis, systemic mastocytosis with associated hematological neoplasm, or mast cell leukemia**.

Guidelines

Rydapt is discussed in the National Comprehensive Cancer Network (NCCN) guidelines:[2]

- **Acute Myeloid Leukemia:** NCCN guidelines (version 1.2023 – March 3, 2023) recommend Rydapt + standard dose cytarabine and daunorubicin among the treatment options for induction, re-induction, consolidation, and post-induction therapy and for relapsed/refractory disease for patients with *FLT3-ITD/TKD* mutation (category 2A).[3] It was noted that while Rydapt was not FDA-approved for maintenance therapy, the pivotal trial was designed for consolidation and maintenance for a total of 12 months.
- **Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Fusion Genes:** NCCN guidelines (version 2.2022 – October 18, 2022) recommend Rydapt for patients with *FGFR1* or *FLT3* rearrangements in chronic phase or blast phase (category 2A).[4] Rydapt is also recommended for treatment in combination with induction chemotherapy followed by allogeneic hematopoietic cell transplantation (if eligible) for lymphoid, myeloid or mixed lineage neoplasms with eosinophilia and *FGFR1* or *FLT3* rearrangements in blast phase (category 2A).
- **Systemic Mastocytosis:** NCCN guidelines (version 2.2022 – October 18, 2022) recommend Rydapt for the treatment of aggressive systemic mastocytosis, systemic mastocytosis with an associated hematologic neoplasm, and mast cell leukemia (all category 2A).[5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Rydapt. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rydapt is recommended in those who meet one of the following criteria:

FDA-Approved Indications

14. **Acute Myeloid Leukemia.** Approve for 1 year if the patient meets the following criteria (A and B):
    A) Patient is ≥ 18 years of age; AND
    B) Patient has *FLT3* mutation-positive disease as detected by an approved test.

15. **Aggressive Systemic Mastocytosis.** Approve for 1 year if the patient is ≥ 18 years of age.

16. **Systemic Mastocytosis Associated with Acute Hematologic Neoplasm.** Approve for 1 year if the patient is ≥ 18 years of age.

17. **Mast Cell Leukemia.** Approve for 1 year if the patient is ≥ 18 years of age.

Other Uses With Supportive Evidence

18. **Myeloid or Lymphoid Neoplasms.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
    - Patient is ≥ 18 years of age; AND
    - Patient has eosinophilia; AND
    - Patient meets one of the following (i or ii):
      - Patient has an *FGFR1* rearrangement; OR
      - Patient has an *FLT3* rearrangement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rydapt is not recommended in the following situations:

20. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

12. Rydapt® capsules [prescribing information]. East Hanover, NJ: Novartis; November 2021.
13. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 7, 2023. Search term: midostaurin.
14. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 1.2023 – March 3, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 7, 2023.
15. The NCCN Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes Clinical Practice Guidelines in Oncology (version 2.2022 – October 18, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 7, 2023.
16. The NCCN Systemic Mastocytosis Clinical Practice Guidelines in Oncology (version 2.2022 – October 18, 2022). © 2022 National Comprehensive Cancer Network. Available at http://www.nccn.org. Accessed on March 7, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Scemblix Prior Authorization Policy
- Scemblix® (asciminib tablets – Novartis)

REVIEW DATE: 05/31/2023

OVERVIEW

Scemblix, a kinase inhibitor, is indicated for the following uses in adults:[1]

- **Chronic myeloid leukemia** (CML), Philadelphia chromosome positive (Ph+), chronic phase, previously treated with two or more tyrosine kinase inhibitors. This indication is approved under accelerated approval based on major molecular response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).
- **CML**, Ph+, chronic phase with the T315I mutation.

Guidelines

Scemblix is discussed in guidelines from National Comprehensive Cancer Network (NCCN):

- **CML:** NCCN guidelines (version 2.2023 – April 13, 2023) state that for patients with chronic phase CML with a low risk score, the primary treatment recommended includes a first-generation TKI (imatinib), or a second-generation TKI (Bosulif® [bosutinib tablets], Sprycel® [dasatinib tablets], or Tasigna® [nilotinib capsules] {all category 1}).[2] For patients with chronic phase CML with an intermediate or high risk score, a second-generation TKI is preferred (Bosulif [category 1], Sprycel [category 1], or Tasigna [category 1]). A first-generation TKI (imatinib) is an alternative (category 2A). Iclusig® (ponatanib tablets) is an option for patients with a T315I mutation and/or chronic phase CML with resistance or intolerance to at least two prior TKIs or for patients with accelerated-phase CML or blast-phase CML for whom no other TKI is indicated (category 2A). Scemblix® (asciminib tablets) is a treatment option for chronic phase CML (Ph+or BCR-ABL1 positive) in patients with the T315I mutation and/or chronic phase CML with resistance or intolerance to at least two prior TKIs (category 2A). Scemblix is contraindicated for use in patients with the following mutations: A337T and P465S.
- **Myeloid/Lympoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions:** NCCN guidelines (version 1.2023 – May 19, 2023) recommend Scemblix as "other recommended regimens" for *ALB1* rearrangements in chronic phase or blast phase (category 2A). It is also recommended as treatment in combination with acute lymphoblastic leukemia or acute myeloid leukemia-type induction chemotherapy followed by allogeneic hematopoietic stem cell transplantation (HSCT) [if eligible] for lymphoid, myeloid, or mixed lineage neoplasms with eosinophilia and *ABL1* rearrangement in blast phase (category 2A).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Scemblix. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Scemblix is recommended in those who meet the following criteria:

FDA-Approved Indication

19. Chronic Myeloid Leukemia. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has Philadelphia chromosome-positive chronic myeloid leukemia; AND
- **C)** Patient meets one of the following (i or ii):
  - **i.** The chronic myeloid leukemia is T315I-positive, OR
  - **ii.** Patient has tried at least two other tyrosine kinase inhibitors indicated for use in Philadelphia chromosome-positive chronic myeloid leukemia.
    Note: Examples of tyrosine kinase inhibitors include imatinib tablets, Bosulif (bosutinib tablets), Iclusig (ponatinib tablets), Sprycel (dasatinib tablets), and Tasigna (nilotinib capsules).

Other Uses with Supportive Evidence

2. Myeloid/Lymphoid Neoplasms with Eosinophilia. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The tumor has an *ABL1* rearrangement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Scemblix is not recommended in the following situations:

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

16. Scemblix® tablets [prescribing information]. East Hanover, NJ: Novartis; October 2021.
17. The NCCN Chronic Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 2.2023 – April 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 25, 2023.
18. The NCCN Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes Clinical Practice Guidelines in Oncology (version 1.2023 – May 19, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 25, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Sorafenib Prior Authorization Policy
- Nexavar® (sorafenib tablets – Bayer/Onyx, generic)

REVIEW DATE: 06/07/2023

OVERVIEW

Sorafenib, a kinase inhibitor, is indicated for the treatment of the following uses:[1]
- **Differentiated thyroid carcinoma**, locally recurrent or metastatic, progressive disease that is refractory to radioactive iodine treatment.
- **Hepatocellular carcinoma** that is unresectable.
- **Renal cell carcinoma** that is advanced.

Guidelines

Sorafenib is discussed in the guidelines from the National Comprehensive Cancer Network (NCCN):[2]
- **Acute Myeloid Leukemia**: NCCN guidelines (version 3.2023 – April 5, 2023) recommend sorafenib + hypomethylating agents (azacitidine or decitabine) for *FLT3*-ITD positive disease for treatment induction or post-induction therapy for patients ≥ 60 years of age and for relapsed/refractory disease (category 2A).[3] Single-agent sorafenib is recommended as maintenance therapy for patients who are post-allogeneic stem cell transplantation, in remission, and have a *FLT3*-ITD mutation (category 2A).
- **Bone Cancer**: NCCN guidelines (version 3.2023 – April 4, 2023) recommend sorafenib as a systemic therapy agent, "useful in certain circumstances", for recurrent chordoma (category 2A).[4] It also recommends sorafenib for osteosarcoma as a second-line therapy for relapsed/refractory or metastatic disease as a "preferred regimen" (category 2A) and as "other recommended regimens" in combination with everolimus [category 2B].
- **Gastrointestinal Stromal Tumor**: NCCN guidelines (version 1.2023 – March 13, 2023) recommend sorafenib (category 2A) as an additional option, "useful in certain circumstances", after failure on approved therapies.[5] The first-line preferred therapies are imatinib or Ayvakit™ (avapritinib tablets; for patients with *PDGFRA* exon 18 mutation, including the *PDGFRA* D842V mutation); second-line therapy is sunitinib or Sprycel® (dasatinib tablets) [for patients with *PDGFRA* exon 18 mutation that are insensitive to imatinib (including the *PDGFRA* D842V mutation); third-line therapy is Stivarga® (regorafenib tablets); fourth-line therapy is Qinlock® (ripretinib tablets).
- **Hepatocellular Carcinoma**: NCCN guidelines (version 1.2023 – March 10, 2023) recommend sorafenib as a first-line systemic therapy option as "other recommended regimens" for Child-Pugh Class A (category 1) or Child Pugh Class B7 (category 2A) and as a subsequent-line therapy if disease progression for Child Pugh Class A or B7 (category 2A) for unresectable, inoperable, or metastatic hepatocellular carcinoma.[6] The guidelines note that there is limited safety data available for Child-Pugh Class B or C patients, and the dosing is uncertain; this drug should be used with extreme caution in patients with elevated bilirubin levels. The impact of sorafenib on patients potentially eligible for transplant is unknown.
- **Kidney Cancer**: NCCN guidelines (version 4.2023 – January 18, 2023) have removed sorafenib as a treatment option for kidney cancer.[7]
- **Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions**: NCCN guidelines (version 1.2023 – May 19, 2023) recommend sorafenib for myeloid/lymphoid neoplasms with *FLT3* rearrangements (category 2A).[8]

- **Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer**: NCCN guidelines (version 2.2023 – June 2, 2023) recommend sorafenib + topotecan (category 2A) as other recommended regimen option as recurrence therapy for platinum-resistant disease.[9]
- **Soft Tissue Sarcoma**: NCCN guidelines (version 2.2023 – April 25, 2023) recommend sorafenib as single-agent therapy under "useful in certain circumstances" for angiosarcoma (category 2A); sorafenib as a "preferred" single-agent regimen for desmoid tumors (aggressive fibromatosis) (category 1) and for solitary fibrous tumor (category 2A).[10]
- **Thyroid Carcinoma**: NCCN guidelines (version 2.2023 – May 18, 2023) for differentiated thyroid carcinoma recommend sorafenib as "other recommended regimens" for progressive and/or symptomatic disease for locally recurrent, advanced, and/or metastatic disease not amenable to radioactive iodine therapy (category 1).[11] Sorafenib can be considered for treatment of progressive or symptomatic medullary thyroid disease if clinical trials or preferred systemic therapy options are not available or appropriate, or if there is progression on preferred systemic therapy options.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of sorafenib. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of sorafenib is recommended in those who meet one of the following criteria:

FDA-Approved Indications

20. Hepatocellular Cancer. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has unresectable or metastatic disease.

21. Renal Cell Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has relapsed or advanced disease; AND
- **C)** Patient has clear cell histology AND
- **D)** Patient has tried at least one systemic therapy.
  Note: Examples of systemic therapy include Inlyta (axitinib tablets), Votrient (pazopanib tablets), sunitinib, Cabometyx (cabozantinib tablets).

22. Thyroid Carcinoma, Differentiated. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has differentiated thyroid carcinoma; AND
  Note: Examples of differentiated thyroid carcinoma include papillary, follicular, and oncocytic carcinoma (formerly Hürthle cell carcinoma).
- **C)** The disease is refractory to radioactive iodine therapy.

Other Uses with Supportive Evidence

~~23.~~ Acute Myeloid Leukemia. Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) Patient is ≥ 18 years of age; AND
B) Patient has *FLT3*-ITD mutation-positive disease as detected by an approved test; AND
C) Patient meets one of the following criteria (i or ii):
i. This medication is used in combination with azacitidine or decitabine; OR
ii. Patient has had an allogeneic stem cell transplant and is in remission.

5. **Bone Cancer.** Approve for 1 year if the patient meets the following criteria (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient meets ONE of the following criteria (i or ii):
i. Patient has recurrent chordoma; OR
ii. Patient meets both of the following criteria (a and b):
a) Patient has osteosarcoma; AND
b) Patient has tried one systemic chemotherapy regimen.
Note: Examples of a systemic chemotherapy regimen contain one of more of the following products: cisplastin, doxorubicin, methotrexate, or ifosfamide.

6. **Gastrointestinal Stromal Tumor.** Approve for 1 year if the patient meets the following criteria (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient has previously tried each of the following (i, ii, iii, and iv):
i. One of imatinib or Ayvakit (avapritinib tablets); AND
ii. One of sunitinib or Sprycel (dasatinib tablets); AND
iii. Stivarga (regorafenib tablets); AND
iv. Qinlock (ripretinib tablets).

7. **Myeloid/Lymphoid Neoplasms with Eosinophilia.** Approve for 1 year if the patient meets the following criteria (A and B):
C) Patient is ≥ 18 years of age; AND
D) The tumor has an *FLT3* rearrangement.

8. **Ovarian, Fallopian Tube, Primary Peritoneal Cancer**. Approve for 1 year if the patient meets the following criteria (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patient has platinum-resistant disease; AND
C) Sorafenib is used in combination with topotecan.

9. **Soft Tissue Sarcoma.** Approve for 1 year if the patient meets the following criteria (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient has ONE of the following diagnoses (i, ii, or iii):
i. Angiosarcoma; OR
ii. Desmoid tumors (aggressive fibromatosis); OR
iii. Solitary Fibrous Tumor/Hemangiopericytoma.

10. **Thyroid Carcinoma, Medullary.** Approve for 1 year if the patient meets the following criteria (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient has tried at least one systemic therapy.
Note: Examples of systemic therapy include: Caprelsa (vandetanib tablets), Cometriq (cabozantinib capsules), Retevmo (selpercatinib capsules), and Gavreto (pralsetinib capsules).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nexavar is not recommended in the following situations:

21. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

36. Sorafenib® tablets [prescribing information]. Wayne, NJ: Bayer; July 2022.
37. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 05, 2023. Search term: sorafenib
38. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 3.2023 – April 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 6, 2023.
39. The NCCN Bone Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – April 4, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 6, 2023.
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41. The NCCN Hepatocellular Carcinoma Clinical Practice Guidelines in Oncology (version 1.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 6, 2023.
42. The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – January 18, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 6, 2023.
43. The NCCN Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions Clinical Practice Guidelines in Oncology (version 1.2023 – May 19, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 6, 2023.
44. The NCCN Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – June 2, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 6, 2023.
45. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 6, 2023.
46. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (version 2.2023 – May 18, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 6, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Sprycel Prior Authorization Policy
- Sprycel® (dasatinib tablets – Bristol-Myers Squibb)

REVIEW DATE: 05/31/2023

OVERVIEW

Sprycel, a tyrosine kinase inhibitor (TKI), is indicated for the following uses:[1]

- **Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL)**:
  - In adults with resistance or intolerance to prior therapy.
  - In newly diagnosed pediatric patients ≥ 1 year of age in combination with chemotherapy.
- **Ph+ chronic myeloid leukemia (CML)**:
  - Chronic phase in newly diagnosed adults.
  - Chronic phase, accelerated, or myeloid or lymphoid blast phase, in adults with resistance or intolerance to prior therapy that included imatinib.
  - Chronic phase, in pediatric patients ≥ 1 year of age.

Guidelines

Sprycel is addressed in guidelines from National Comprehensive Cancer Network (NCCN):

- **ALL:** NCCN guidelines for adults and adolescents (version 1.2022 – April 4, 2022) recommend Sprycel for Ph+ disease in many different clinical circumstances (e.g., induction, consolidation therapy, maintenance, or relapsed or refractory disease) [category 2A].[2] TKIs in combination with other agents (e.g., chemotherapy or corticosteroids) are recommended for induction therapy for Ph+ ALL. TKIs have also been incorporated into consolidation and maintenance therapy, as well as in the relapsed/refractory setting (category 2A). TKI options include: Bosulif® (bosutinib tablets), Sprycel, imatinib, Tasigna (nilotinib capsules), or Iclusig® (ponatinib tablets) [category 2A]. NCCN panel notes that not all TKIs have been directly studied within the context of each specific regimen and there are limited data for Bosulif in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance and disease-related features. For adults and adolescents, Iclusig has activity against T315I mutations and/or in whom no other TKI is indicated (category 2A). NCCN guidelines for pediatric ALL (version 2.2023 – March 10, 2023) feature Sprycel prominently in a variety of clinical scenarios (mainly category 2A recommendations).[3]
- **Bone Cancer:** NCCN guidelines (version 3.2023 – April 4, 2023) recommend Sprycel for patients with chondrosarcoma as "other recommended regimens" for a patient with metastatic and widespread disease (category 2A).[4] Sprycel is also recommended for chordoma as "other recommended regimens" (category 2A).
- **CML:** NCCN guidelines (version 2.2023 – April 13, 2023) recommend Sprycel as a preferred primary treatment for newly diagnosed chronic phase Ph+ CML with a low-, intermediate-, or high-risk score (category 1).[5] Sprycel is also recommended as an alternative TKI treatment (after primary treatment with imatinib, Bosulif® [bosutinib tablets], or Tasigna® [nilotinib capsules]) for BCR::ABL1 transcript levels (category 2A). Sprycel is also recommended in a variety of other situations, including post-allogeneic hematopoietic stem cell transplant (category 2A).
- **Gastrointestinal Stromal Tumor:** NCCN guidelines (version 1.2023 – March 13, 2023) recommend Sprycel as a second-line therapy as "other recommended regimens" for unresectable, progressive or metastatic disease in patients with platelet-derived growth factor receptor alpha *[PDGFRA]* exon 18 mutations that are insensitive to imatinib (including the PDGFRA D842V mutation).[6]

- **Melanoma: Cutaneous**: NCCN guidelines (version 2.2023 – March 10, 2023) recommend Sprycel as "useful in certain circumstances" for metastatic or unresectable disease with an activating *KIT* mutation as second-line or subsequent therapy for disease progression, intolerance, and/or projected risk of progression with *BRAF*-targeted therapy.[7]
- **Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions:** NCCN guidelines (version 1.2023 –May 19, 2023) list Sprycel as a preferred therapy under "other recommended regimens" for chronic phase or blast phase disease with an *ABL1* rearrangement (category 2A).[8,9]. It is also recommended as treatment in combination with ALL- or acute myeloid leukemia-type induction chemotherapy followed by allogeneic hematopoietic stem cell transplantation (HCT) (if eligible) for lymphoid, myeloid or mixed lineage neoplasms with eosinophilia and *ABL1* rearrangement in blast phase (category 2A).[9]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Sprycel. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Sprycel is recommended in those who meet one of the following criteria:

FDA-Approved Indications

3. **Acute Lymphoblastic Leukemia.** Approve for 1 year if the patient has Philadelphia chromosome-positive acute lymphoblastic leukemia.

4. **Chronic Myeloid Leukemia.** Approve for 1 year if the patient has Philadelphia chromosome-positive chronic myeloid leukemia.

Other Uses with Supportive Evidence

3. **Bone Cancer.** Approve for 1 year if the patient meets the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has chondrosarcoma or chordoma.

4. **Gastrointestinal Stromal Tumor.** Approve for 1 year if the patient meets the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has tried imatinib or Ayvakit (avapritinib tablets).

5. **Melanoma, Cutaneous.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
   E) Patient is ≥ 18 years of age; AND
   F) Patient has metastatic or unresectable disease; AND
   G) Patient has an activating *KIT* mutation; AND
   H) Patient has tried at least one systemic regimen.
   Note: Examples of a systemic regimen include: Opdivo (nivolumab intravenous infusion) + Yervoy (ipilimumab intravenous infusion), Opdivo + Opdualag (nivolumab/relatlimab-rmbw

intravenous infusion), Keytruda (pembrolizumab intravenous infusion), Opdivo, Tafinlar (dabrafenib capsules) + Mekinist (trametinib tablets), Zelboraf (vemurafenib tablets) + Cotellic (cobimetinib tablets), Braftovi (encorafenib capsules) + Mektovi (binimetinib tablets).

6. Myeloid/Lymphoid Neoplasms with Eosinophilia. Approve for 1 year if the patient meets the following criteria (A and B):
A) Patient is ≥ 18 years of age; AND
B) The tumor has an *ABL1* rearrangement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sprycel is not recommended in the following situations:

22. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

47. Sprycel® tablets [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; February 2023.
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50. The NCCN Bone Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – April 4, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 10, 2023.
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53. The NCCN Melanoma: Cutaneous Clinical Practice Guidelines in Oncology (version 2.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 10, 2023.
54. The NCCN Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions Clinical Practice Guidelines in Oncology (version 1.2023 – May 19, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 10, 2023.
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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Stivarga Prior Authorization Policy
- Stivarga® (regorafenib tablets – Bayer)

REVIEW DATE: 03/08/2023

OVERVIEW

Stivarga, a kinase inhibitor, is indicated for the following uses:[1]

- **Colorectal cancer**, metastatic, in patients who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor (VEGF) therapy, and, if *RAS* wild-type, an anti-epidermal growth factor receptor (EGFR) therapy.
- **Gastrointestinal stromal tumor**, locally advanced, unresectable, or metastatic in patients who have been previously treated with imatinib and sunitinib.
- **Hepatocellular carcinoma**, in patients who have been previously treated with sorafenib.

Guidelines

Stivarga is discussed in National Comprehensive Cancer Network (NCCN) guidelines:[2]

- **Bone Cancer**: NCCN guidelines (version 2.2023 – September 28, 2022) recommend Stivarga as a single agent "Preferred Regimen" for second-line therapy for relapsed/refractory or metastatic disease for patients with osteosarcoma (category 1).[3]
- **Central Nervous System Cancers**: NCCN guidelines (version 2.2022 – September 29, 2022) recommend Stivarga as a single agent "Preferred Regimen" for the treatment of recurrent glioblastoma (category 2A).[4]
- **Colon Cancer and Rectal Cancer**: NCCN guidelines (colon cancer [version 3.2022 – January 25, 2023] and rectal cancer [version 4.2022 – January 25, 2023]) recommend Stivarga as subsequent therapy as a single agent for advanced or metastatic disease not previously treated with Stivarga in patients who have progressed through all available regimens except Stivarga or Lonsurf® (trifluridine and tipiracil tablets) with or without bevacizumab.[5,6] Stivarga may be given before or after Lonsurf. Appendiceal adenocarcinoma are treated similarly to colon cancer.
- **Gastrointestinal Stromal Tumors**: NCCN guidelines (version 2.2022 – September 1, 2022) recommend Stivarga as a "Preferred Regimen" for treatment of unresectable, recurrent, or metastatic disease with widespread, systemic progression after single-agent therapy with imatinib and sunitinib or Sprycel (dasatinib tablets) [category 1].[7] Stivarga in combination with everolimus tablets is recommended as "Useful in Certain Circumstances" for unresectable, recurrent, or metastatic disease after failure on approved therapies. Stivarga is also recommended as a special consideration for unresectable, *succinate dehydrogenase*-deficient disease.[7]
- **Hepatobiliary Cancers**: NCCN guidelines (version 5.2022 – January 13, 2023) recommend Stivarga for subsequent treatment as a single agent for patients with hepatocellular carcinoma (adenocarcinoma) [Child-Pugh Class A only] and disease progression for the following uses (all are category 1): in patients who are not transplant candidates with unresectable disease; in patients who have liver-confined disease, inoperable by performance status or comorbidity or with minimal or uncertain extrahepatic disease; or in patients who have extensive liver tumor burden or metastatic disease.[8] Stivarga is also recommended as subsequent treatment as a single agent for progression on or after systemic treatment for unresectable or metastatic disease (category 2B).[8]
- **Soft Tissue Sarcoma**: NCCN guidelines (version 2.2022 – May 17, 2022) recommend Stivarga as a single-agent subsequent therapy for patients with non-adipocytic sarcoma with

advanced/metastatic disease, advanced/metastatic pleomorphic rhabdomyosarcoma, or angiosarcoma (all category 2A).[9]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Stivarga. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Stivarga is recommended in those who meet one of the following criteria:

FDA-Approved Indications

24. Colon, Rectal and Appendiceal Cancer. Approve for 1 year if the patient meets all of the following criteria (A, B, C, D, E, and F):
- **L)** Patient is ≥ 18 years of age; AND
- **M)** Patient has advanced or metastatic disease; AND
- **N)** Patient has been previously treated with a fluoropyrimidine (e.g., capecitabine, 5-fluorouracil [5-FU]); AND
- **O)** Patient has been previously treated with oxaliplatin; AND
- **P)** Patient has been previously treated with irinotecan; AND
- **Q)** Patient meets one of the following criteria (i or ii):
  - **i.** Patient's tumor or metastases are wild-type *RAS* (*KRAS* wild-type and *NRAS* wild-type) and the patient meets one of the following criteria (a or b):
    Note: This includes tumors or metastases that are *KRAS* and *NRAS* mutation-negative.
    - **a)** The patient has tried Erbitux (cetuximab intravenous infusion) or Vectibix (panitumumab intravenous infusion); OR
    - **b)** The patient's tumor did not originate on the left side of the colon (from the splenic fixture to rectum); OR
  - **ii.** The patient's tumor has or metastases have a *RAS* mutation (either *KRAS* mutation or *NRAS* mutation).

2. Gastrointestinal Stromal Tumor. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has tried both of the following (i and ii):
  - **i.** Imatinib or Ayvakit (avapritinib tablets); AND
  - **ii.** Sunitinib or Sprycel (dasatinib tablets).

3. Hepatocellular Carcinoma. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has been previously treated with one systemic regimen.
  Note: Examples of a systemic regimen include: Tecentriq (atezolizumab intravenous infusion), bevacizumab, sorafenib, Lenvima (lenvatinib capsules), Opdivo (nivolumab intravenous infusion), Imjudo (tremelimumab-actl intravenous infusion), Imfinzi (durvalumab intravenous infusion).

Other Uses with Supportive Evidence

4. **Glioblastoma.** Approve for 1 year if the patient meets the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has recurrent disease.

5. **Osteosarcoma.** Approve for 1 year if the patient meets all of the following criteria (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has relapsed/refractory or metastatic disease; AND
   C) Patient has tried one systemic chemotherapy regimen.
   Note: Examples of a systemic chemotherapy regimen contain one of more of the following products: cisplastin, doxorubicin, methotrexate, or ifosfamide.

6. **Soft Tissue Sarcoma.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has advanced or metastatic disease; AND
   C) Patient has one of the following (i, ii, or iii):
      i. Non-adipocytic sarcoma; OR
      ii. Pleomorphic rhabdomyosarcoma; OR
      iii. Angiosarcoma.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Stivarga is not recommended in the following situations:

23. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Stivarga® tablets [prescribing information]. Whippany, NJ: Bayer; December 2020.
2. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 5, 2023. Search term: regorafenib.
3. The NCCN Bone Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – September 28, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 5, 2023.
4. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 2.2022 – September 29, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 6, 2023.
5. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 3.2022 – January 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 6, 2023.
6. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 4.2022 – January 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 6, 2023.
7. The NCCN Gastrointestinal Stromal Tumors Clinical Practice Guidelines in Oncology (version 2.2022 – September 1, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 5, 2023.
8. The NCCN Hepatobiliary Cancers Clinical Practice Guidelines in Oncology (version 5.2022 – January 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 6, 2023.
9. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 2.2022 – May 17, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 5, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Sunitinib Prior Authorization Policy
- Sutent® (sunitinib malate capsules – Pfizer; generic)

REVIEW DATE: 06/28/2023

OVERVIEW

Sunitinib, a kinase inhibitor, is indicated in adults for the following uses:[1]

- **Gastrointestinal stromal tumor (GIST)**, after disease progression on or intolerance to imatinib mesylate tablets.
- **Pancreatic neuroendocrine tumors**, that is progressive and well-differentiated in patients with unresectable locally advanced or metastatic disease.
- **Renal cell carcinoma,** advanced, and for the adjuvant treatment of adult patients at high risk of recurrent renal cell carcinoma following nephrectomy.

Guidelines

Sunitinib is discussed in the guidelines from the National Comprehensive Cancer Network (NCCN):[2]

- **Bone Cancer**: NCCN guidelines (version 3.2023 – April 4, 2023) recommend sunitinib as a systemic therapy agent for recurrent chordoma (category 2A).[3]
- **Central Nervous System Cancers**: NCCN guidelines (version 1.2023 – March 24, 2023) recommend sunitinib for meningioma for surgically inaccessible recurrent or progressive disease when radiation is not possible (category 2B).[4]
- **Gastrointestinal Stromal Tumor**: NCCN guidelines (version 1.2023 – March 13, 2023) recommend sunitinib as preferred second-line therapy for unresectable, progressive, or metastatic disease (category 1).[5] The first line therapies include imatinib or Ayvakit™ (avapritinib tablets; for GIST with *PDGFRA* exon 18 mutation that are insensitive to imatinib, including the *PDGFRA* D842V mutation).[5] The guidelines also state in a footnote that for unresectable disease, sunitinib, Stivarga® (regorafenib tablets) and Votrient® (pazopanib tablets) are special considerations for succinate dehydrogenase (SDH)-deficient GIST (category 2A). Sunitinib is also recommended in combination with everolimus as "useful in certain circumstances" for unresectable, recurrent/progressive, or metastatic disease after progression on approved therapies (category 2A).
- **Kidney Cancer**: NCCN guidelines (version 4.2023 – January 18, 2023) recommend single-agent sunitinib as adjuvant treatment following nephrectomy for stage 3 disease with clear cell histology (category 3).[6] NCCN guidelines also recommend single-agent sunitinib for relapse or stage IV disease as a first-line and subsequent therapy option for clear cell histology and as a "preferred" systemic therapy option for non-clear cell histology (category 2A).[6]
- **Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes**: NCCN guidelines (version 1.2023 – May 19, 2023) recommend sunitinib for myeloid/lymphoid neoplasms with *FLT3* rearrangements (category 2A).[7]
- **Neuroendocrine and Adrenal Tumors**: NCCN guidelines (version 2.2022 – December 21, 2022) recommend sunitinib as a "preferred" single-agent for the management of recurrent, locoregional advanced disease and/or distant metastatic disease (category 1 for progressive disease; category 2A for all others).[8] NCCN guidelines also recommend for treatment (pancreas only) for unresectable locally advanced/metastatic disease with favorable biology (e.g. relatively low Ki-67 [<55%], positive SSR-based PET imaging) that has clinically significant tumor burden or evidence of progression (category 2A). Sunitinib is also recommended as a single-agent for locally unresectable or distant metastatic pheochromocytoma and paraganglioma.[8]

- **Soft Tissue Sarcoma**: NCCN guidelines (version 2.2023 – April 25, 2023) recommend sunitinib as single-agent therapy as "useful in certain circumstances" for angiosarcoma (category 2A).[9] The guidelines also recommend sunitinib as a preferred single-agent therapy for alveolar soft part sarcoma and for solitary fibrous tumor (both category 2A).[9]
- **Thymomas and Thymic Carcinomas**: NCCN guidelines (version 1.2023 – December 15, 2022) recommend single agent sunitinib as second-line systemic therapy for thymic carcinoma (category 2A).[10]
- **Thyroid Carcinoma**: NCCN guidelines (version 2.2023 – May 18, 2023) recommend sunitinib as one of the kinase inhibitors to be considered if clinical trials or other systemic therapies are not available or appropriate for the treatment of progressive and/or symptomatic iodine refractory thyroid cancer.[11] This recommendation is for follicular, oncocytic (formerly Hürthle cell carcinoma), and papillary cancer subtypes (all category 2A). Sunitinib can be considered for treatment of progressive or symptomatic medullary thyroid disease if clinical trials or preferred systemic therapy options are not available or appropriate, or if there is progression on preferred systemic therapy options (category 2A).[11]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of sunitinib. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sunitinib is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Gastrointestinal Stromal Tumor.** Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets one of the following criteria (i or ii):
   - **i.** Patient has tried imatinib or Ayvakit (avapritinib tablets); OR
   - **ii.** Patient has succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumor.

2. **Neuroendocrine Tumors of the Pancreas.** Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has advanced or metastatic disease.

3. **Renal Cell Cancer.** Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has relapsed or advanced disease.

Other Uses with Supportive Evidence

4. **Bone Cancer.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has recurrent chordoma.

5. **Meningioma.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has recurrent or progressive disease.

6. **Myeloid/Lymphoid Neoplasms.** Approve for 1 year if the patient meets the following (A, B, and C):
   E) Patient is ≥ 18 years of age; AND
   F) Patient has eosinophilia; AND
   G) The tumor has an *FLT3* rearrangement.

7. **Pheochromocytoma/Paraganglioma.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has unresectable or metastatic disease.

8. **Soft Tissue Sarcoma.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has one of the following diagnosis (i, ii, or iii):
      i. Alveolar soft part sarcoma; OR
      ii. Angiosarcoma; OR
      iii. Solitary fibrous tumor/Hemangiopericytoma.

9. **Thymic Carcinoma.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has tried at least one systemic chemotherapy regimen.
   Note: Examples of a systemic chemotherapy regimen include one or more of the following products: carboplatin, paclitaxel, cisplatin, doxorubicin, cyclophosphamide, or etoposide.

10. **Thyroid Carcinoma, Differentiated.** Approve for 1 year if the patient meets the following (A, B, and C):
    A) Patient is ≥ 18 years of age; AND
    B) Patient has differentiated thyroid carcinoma; AND
    Note: Examples of differentiated thyroid carcinoma include papillary, follicular, and oncocytic carcinoma (formerly Hürthle cell carcinoma).
    C) Patient is refractory to radioactive iodine therapy.

11. **Thyroid Carcinoma, Medullary.** Approve for 1 year if the patient meets the following (A and B):
    A) Patient is ≥ 18 years of age; AND
    B) Patient has tried at least one systemic therapy.
    Note: Examples of systemic therapy include: Caprelsa (vandetanib tablets), Cometriq (cabozantinib capsules), Retevmo (selpercatinib capsules), and Gavreto (pralsetinib capsules).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of sunitinib is not recommended in the following situations:

24. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

56. Sutent® capsules [prescribing information]. New York, NY: Pfizer; August 2021.
57. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 16, 2023. Search term: sunitinib.
58. The NCCN Bone Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – April 4, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 19, 2023.
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61. The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – January 18, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 19, 2023.
62. The NCCN Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes Clinical Practice Guidelines in Oncology (version 1.2023 – May 19, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 19, 2023.
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64. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 19, 2023.
65. The NCCN Thymomas and Thymic Carcinomas Clinical Practice Guidelines in Oncology (version 1.2023 – December 15, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 19, 2023.
66. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (version 2.2023 – May 18, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 19, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tabrecta Prior Authorization Policy
- Tabrecta® (capmatinib tablets – Novartis)

REVIEW DATE: 02/01/2023

OVERVIEW

Tabrecta, a kinase inhibitor, is indicated for the treatment of adults with metastatic **non-small cell lung cancer (NSCLC)** whose tumors have a mutation that leads to mesenchymal-epithelial transition (*MET*) exon 14 skipping as detected by an FDA-approved test.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) NSCLC guidelines (version 1.2023 – December 22, 2022) recommend Tabrecta as a first-line or subsequent line treatment option for patients with advanced or metastatic NSCLC who are positive for *MET* exon 14 skipping mutations or high-level *MET* amplification.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tabrecta. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tabrecta is recommended in those who meet the following criteria:

FDA-Approved Indication

5. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has advanced or metastatic disease; AND
- **C)** Patient meets one of the following criteria (i or ii):
  - **i.** Patient has mesenchymal epithelial transition (*MET*) exon 14 skipping mutations as detected by an approved test; OR
  - **ii.** Patient has high-level *MET* amplification as detected by an approved test.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tabrecta is not recommended in the following situations:

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

26. Tabrecta® tablets [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; August 2022.
27. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on January 27, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tafinlar Prior Authorization Policy
- Tafinlar® (dabrafenib capsules and tablets for oral suspension – Novartis)

REVIEW DATE: 04/05/2023; selected revision 09/13/2023

OVERVIEW

Tafinlar, a BRAF inhibitor, is indicated for the following uses:[1]

- **Low-grade glioma,** in combination with Mekinist, for the treatment of pediatric patients ≥ 1 year of age with a BRAF V600E mutation who require systemic therapy.
- **Melanoma**, in the following situations:[1]
  - As a single agent for unresectable or metastatic disease with *BRAF V600E* mutation as detected by an FDA-approved test.
  - In combination with Mekinist® (trametinib tablets and oral solution), for unresectable or metastatic disease with a *BRAF V600E* or *V600K* mutation, as detected by an FDA-approved test.
  - In combination with Mekinist, as adjuvant treatment of *BRAF V600E* or *V600K* mutation-positive disease as detected by an FDA-approved test, with involvement of the lymph node(s), following complete resection.
- **Non-small cell lung cancer**, in combination with Mekinist for disease that has the *BRAF V600E* mutation as detected by an FDA-approved test.
- **Solid tumors - unresectable or metastatic**, in combination with Mekinist, for *BRAF V600E* mutation-positive disease, as determined by an FDA-approved test, in patients ≥ 1 year of age who have no satisfactory alternative treatment options.
- **Thyroid cancer**, in combination with Mekinist, for locally advanced or metastatic anaplastic disease with *BRAF V600E* mutation and with no satisfactory locoregional treatment options.

Limitations of Use**:** Tafinlar is not indicated for treatment of patients with colorectal cancer because of the known intrinsic resistance to BRAF inhibition. Tafinlar is not indicated for treatment of patients with wild-type BRAF solid tumors.

Dosing: For the tablet dosage form, Tafinlar has dosing for patients who are adults and for patients who are between 6 and 17 years of age and weigh ≥ 26 kg. The oral solution dosage form also has weight-based dosing for patients ≥ 8 kg.

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines support use in multiple cancers.

- **Central Nervous System Cancers:** Guidelines (version 1.2023 – March 24, 2023) recommend a BRAF/MEK inhibitor combination (i.e., Tafinlar/Mekinist or Zelboraf® [vemurafenib tablets]/Cotellic® [cobimetinib tablets]) for treatment of *BRAF V600E* activation mutations in adults in the following situations: adjuvant treatment of pilocytic astrocytoma, pleomorphic xanthoastrocytoma, or ganglioglioma; recurrent or progressive low-grade glioma, oligodenroglioma, or isocitrate dehydrogenase-2 (*IDH2*)-mutant astrocytoma; and recurrent glioblastoma. BRAF/MEK combination therapy is also recommended for melanoma with brain metastases.[6] Guidelines for pediatric central nervous system (CNS) cancers (version 2.2023 – October 31, 2022) include targeted therapy with Tafinlar + Mekinist as adjuvant therapy or for recurrent or progressive disease, if the cancer has a *BRAF V600E* mutation.[9]

- **Histiocytic Neoplasms:** Guidelines (version 1.2022 – May 20, 2022) recommend Zelboraf as "preferred" or Tafinlar as "other recommended regimen" for *BRAF V600E*-mutated Erdheim-Chester disease, and for multisystem, pulmonary, or CNS Langerhans cell histiocytosis.[5]
- **Melanoma, Cutaneous:** Guidelines (version 2.2023 – March 10, 2023) recommend BRAF/MEK inhibitor combinations among the preferred therapies for first-line and subsequent treatment of metastatic or unresectable melanoma with a *V600*-activating mutation.[2] While combination BRAF/MEK inhibition is preferred, if a combination is contraindicated, monotherapy with a BRAF inhibitor is an option. Tafinlar + Mekinist is also recommended in guidelines as adjuvant therapy (including for nodal recurrence) in some patients with Stage III disease, including use post-surgery or use after complete lymph node dissection. If unacceptable toxicity to Tafinlar/Mekinist, other BRAF/MEK combinations can be considered.
- **Non-Small Cell Lung Cancer:** Guidelines (version 2.2023 – February 17, 2023) list Tafinlar + Mekinist among the first-line therapy and subsequent therapy options for tumors with a *BRAF* mutation.[3] NCCN also notes that monotherapy with a BRAF inhibitor (Tafinlar or Zelboraf) is a treatment option when combination therapy is not tolerated.

The NCCN Compendium[7] recommends use of Tafinlar, in combination with Mekinist, for the following *BRAF V600* positive tumors (all category 2A): High-grade gliomas, ampullary adenocarcinoma, neuroendocrine tumors, pancreatic adenocarcinoma, salivary gland tumors, ovarian/fallopian tube/primary peritoneal cancer, esophageal and esophagogastric junction cancers, gastric cancer, biliary tract cancers, gastrointestinal stromal tumors, brain metastases due to melanoma, and differentiated thyroid carcinoma.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tafinlar. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tafinlar is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Low Grade Glioma.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   - **A)** Patient is ≥ 1 year of age; AND
   - **B)** Patient has *BRAF V600* mutation-positive disease; AND
   - **C)** The medication will be taken in combination with Mekinist (trametinib tablets or oral solution); AND
   - **D)** Patient requires systemic therapy.

2. **Melanoma.** Approve for 1 year if the patient meets the following (A, B, and C):
   - **A)** Patient is ≥ 6 years of age; AND
   - **B)** Patient has unresectable, advanced (including Stage III or Stage IV disease), or metastatic melanoma; AND
     Note: This includes adjuvant treatment in patients with Stage III disease with no evidence of disease post-surgery.
   - **C)** Patient has *BRAF V600* mutation-positive disease.

3. **Non-Small Cell Lung Cancer.** Approve for 1 year if the patient meets the following (A and B)
   A) Patient is ≥ 6 years of age; AND
   B) Patient has *BRAF V600* mutation-positive disease.

4. **Solid Tumors – Unresectable or Metastatic.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   Note: Examples of solid tumors are: biliary tract cancer, brain metastases due to melanoma, high-grade gliomas, ovarian/fallopian tube/primary peritoneal cancer, differentiated thyroid carcinoma, gastrointestinal stromal tumors, gastric cancer, esophageal and esophagogastric junction cancers, salivary gland tumors, pancreatic adenocarcinoma, neuroendocrine tumors, and ampullary adenocarcinoma.
   E) Patient is ≥ 1 year of age; AND
   F) Patient has *BRAF V600* mutation-positive disease; AND
   G) The medication will be taken in combination with Mekinist (trametinib tablets or oral solution); AND
   H) According to the prescriber, the patient has no satisfactory alternative treatment options.

5. **Thyroid Carcinoma, Anaplastic.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   E) Patient is ≥ 6 years of age; AND
   F) Patient has locally advanced or metastatic anaplastic disease; AND
   G) Patient has *BRAF V600* mutation-positive disease; AND
   H) The medication will be taken in combination with Mekinist (trametinib tablets or oral solution), unless intolerant.

Other Uses with Supportive Evidence

6. **Histiocytic Neoplasm.** Approve for 1 year if the patient meets the following (A, B, and C):
   A) Patient is ≥ 6 years of age; AND
   B) Patient meets one of the following (i or ii):
      i. Patient has Langerhans cell histiocytosis AND one of the following (a, b, or c):
         a) Multisystem disease; OR
         b) Pulmonary disease; OR
         c) Central nervous system lesions; OR
      ii. Patient has Erdheim-Chester disease; AND
   C) Patient has *BRAF V600*-mutation positive disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tafinlar is not recommended in the following situations:

1. **Colon or Rectal Cancer.** Tafinlar is not indicated for treatment of patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition.[1]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

34. Tafinlar® capsules and tablets for oral suspension [prescribing information]. East Hanover, NJ: Novartis; August 2023.
35. The NCCN Melanoma: Cutaneous Clinical Practice Guidelines in Oncology (version 2.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on April 3, 2023.
36. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – February 17, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on April 3, 2023.
37. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (version 1.2023 – March 24, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on April 3, 2023.
38. The NCCN Histiocytic Neoplasms Clinical Practice Guidelines in Oncology (version 1.2022 – May 20, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on April 3, 2023.
39. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 1.2023 – March 24, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on April 3, 2023.
40. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 3, 2023. Search term: dabrafenib.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tagrisso Prior Authorization Policy
- Tagrisso® (osimertinib tablets – AstraZeneca)

REVIEW DATE: 01/11/2023

OVERVIEW

Tagrisso, a tyrosine kinase inhibitor, is indicated for the following uses:[1]

- **Non-Small Cell Lung Cancer (NSCLC) – Epidermal growth factor rector (*EGFR*) Mutation-Positive:** First-line treatment of adults with metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.
- **NSCLC – *EGFR* T790M Mutation-Positive:** Treatment of adults with metastatic *EGFR* T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after *EGFR* tyrosine kinase inhibitor (TKI) therapy.
- **NSCLC – *EGFR* Mutation-Positive, Post Tumor Resection:** Adjuvant therapy after tumor resection in adults with NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines for NSCLC (version 1.2023 – December 22, 2022) recommend testing for sensitizing *EGFR* mutations in patients with metastatic disease.[2] The most common *EGFR* mutations are exon 19 deletions and exon 21 (L858R) substitution mutations. Other less common mutations that are also sensitive to *EGFR* tyrosine kinase inhibitors (TKIs) include L861Q, G719X, and S768I. NCCN recommends the *EGFR* TKIs as first-line treatment for patients with advanced or metastatic NSCLC with *EGFR* exon 19 deletions, exon 21 (L858R) substitution mutations, L861Q, G719X, and S768I. Tagrisso is a preferred first-line *EGFR* TKI and is also recommended as subsequent treatment for these patients. The panel recommends T790M (a secondary mutation in *EGFR*) testing in patients who progress on erlotinib tablets, Gilotrif® (afatinib tablets), Iressa® (gefitinib tablets), or Vizimpro® (dacomitinib tablets). If the patient has *EGFR* T790M-positive metastatic NSCLC, Tagrisso may be considered for second-line and beyond (subsequent) therapy. If the disease is *EGFR* T790M-negative, the patient can be continued on the current TKI (i.e., erlotinib, Gilotrif, Iressa, or Vizimpro). Tagrisso is also recommended for use in patients with completely resected stage IB-IIIA *EGFR* (exon 19 deletion, L858R) NSCLC who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tagrisso. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tagrisso is recommended in those who meet one of the following criteria:

FDA-Approved Indications

4. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets the following criteria (A, B and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has advanced or metastatic disease; AND
- **C)** Patient meets one of the following criteria (i or ii):
  - **i.** Patient has sensitizing epidermal growth factor receptor (*EGFR)* mutation-positive disease as detected by an approved test; OR
    Note: Examples of sensitizing *EGFR* mutation-positive non-small cell lung cancer include the following: exon 19 deletions, exon 21 (L858R) substitution mutations, L861Q, G719X, and S768I.
  - **ii.** Patient meets the following criteria (a and b):
    - **a)** Patient has epidermal growth factor receptor (*EGFR*) T790M mutation-positive disease as detected by an approved test; AND
    - **b)** Patient has progressed on treatment with at least one of the *EGFR* tyrosine kinase inhibitors.
      Note: *EGFR* tyrosine kinase inhibitors are erlotinib, Iressa (gefitinib tablets), Vizimpro (dacomitinib tablets), Gilotrif (afatinib tablets).

2. Non-Small Cell Lung Cancer – Post Tumor Resection. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has completely resected disease; AND
- **C)** Patient has *EGFR* exon 19 deletion or exon 21 (L858R) substitution mutation as detected by an approved test; AND
- **D)** Patient meets one of the following criteria (i or ii):
  - **i.** Patient received previous adjuvant chemotherapy; OR
  - **ii.** Patient is ineligible to receive platinum-based chemotherapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tagrisso is not recommended in the following situations:

25. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

41. Tagrisso™ tablets [prescribing information]. Wilmington, DE: AstraZeneca; December 2020.
42. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 9, 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Talzenna Prior Authorization Policy
- Talzenna® (talazoparib capsules – Pfizer)

REVIEW DATE: 12/13/2023

OVERVIEW

Talzenna, a poly (ADP-ribose) polymerase (PARP) inhibitor, is indicated for the following uses:[1]

- **Breast cancer**, for the treatment of deleterious or suspected deleterious germline BReast CAncer susceptibility gene (BRCA)-mutated human epidermal growth factor receptor 2 (HER2)-negative locally-advanced or metastatic breast cancer in adults.
- **Prostate cancer**, for the treatment of homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) in combination with Xtandi® (enzalutamide capsules or tablets) in adults.

GUIDELINES

Talzenna is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):

- **Breast Cancer**: NCCN guidelines (version 5.2023 – December 5, 2023) recommend Talzenna for patients with recurrent unresectable (local or regional) or Stage IV disease breast cancer with hormone receptor-positive, HER2-negative disease with visceral crisis or endocrine-refractory, germline *BRCA1/2* mutation as a "Preferred Regimen" (category 1).[2] Lynparza® (olaparib tablets) is another "Preferred Regimen" in this setting (category 1). There is a footnote which states PARP inhibitors can be considered for a later line for those with *BRCA*1/2 mutation, however, available evidence suggests it is more effective if used earlier. Talzenna is also recommended as a single-agent for recurrent, unresectable, or stage IV HER2-positive disease with a *BRCA1/2* mutation (category 2A). The guidelines note that although Talzenna and Lynparza are FDA-approved for HER2-negative disease, the NCCN Panel supports use of these agents in any subtype associated with a germline *BRCA1/2* mutation. For triple negative breast cancer with germline *BRCA*1/2 mutation, Talzenna and Lynparza are listed as a "Preferred Regimens" in the first-line setting for patients with programmed cell death ligand 1 combined positive score (PD-L1 CPS) < 10 (category 1), and also in the second-line setting (category 1).
- **Prostate Cancer:** NCCN guidelines (version 4.2023 – September 7, 2023) recommend Talzenna + Xtandi for HRR mutation (category 1) as "Useful in Certain Circumstances" in the first-line setting for mCRPC. For patients who have received prior novel hormone therapy and no prior docetaxel therapy, Talzenna + Xtandi is recommended for HRR mutation (category 2B) as "Useful in Certain Circumstances". For patients who have received prior docetaxel therapy and no prior novel hormone therapy, Talzenna + Xtandi is recommended for HRR mutation (category 2A) as "Useful in Certain Circumstances".

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Talzenna. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Talzenna is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. **Breast Cancer.** Approve for 1 year if the patient meets the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has recurrent or metastatic breast cancer; AND
   - **C)** Patients has germline *BRCA* mutation-positive disease.

2. **Prostate Cancer.** Approve for 1 year if the patient meets the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has metastatic castration resistant prostate cancer; AND
   - **C)** Patient meets one of the following criteria (i or ii):
     - **i.** The medication is used concurrently with a gonadotropin-releasing hormone (GnRH) analog; OR
       Note: Examples are leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Vantas (histrelin acetate subcutaneous implant), Firmagon (degarelix acetate subcutaneous injection), Orgovyx (relugolix tablets).
     - **ii.** Patient has had a bilateral orchiectomy; AND
   - **D)** Patient has homologous recombination repair (HRR) gene-mutated disease; AND
     Note: HRR gene mutations include *ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, or RAD51C*
   - **E)** The medication is used in combination with Xtandi (enzalutamide capsules and tablets).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Talzenna is not recommended in the following situations:

26. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

43. Talzenna® capsules [prescribing information]. New York, NY: Pfizer; June 2023.
44. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 5.2023 – December 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 12, 2023.
45. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – September 7, 2023). © 2023National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed December 1, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tasigna Prior Authorization Policy
- Tasigna® (nilotinib capsules – Novartis)

REVIEW DATE: 05/31/2023

OVERVIEW

Tasigna, a tyrosine kinase inhibitor (TKI), is indicated for the following uses:[1]

- **Chronic myeloid leukemia (CML)**, chronic phase, newly diagnosed and Philadelphia chromosome positive (Ph+), in adult and pediatric patients ≥ 1 year of age.
- **CML**, Ph+, chronic phase and accelerated phase, in adults with resistance or intolerance to prior therapy that included imatinib.
- **CML**, Ph+, chronic phase and accelerated phase, in pediatric patients ≥ 1 year of age with resistance or intolerance to prior TKI therapy.

Guidelines

Tasigna is addressed in guidelines from National Comprehensive Cancer Network (NCCN):

- **Acute Lymphoblastic Leukemia (ALL):** NCCN guidelines for adults and adolescents (version 1.2022 – April 4, 2022) recommend Tasigna for Ph+ disease in many different clinical circumstances (e.g., induction, consolidation therapy, maintenance, or relapsed or refractory disease) [category 2A].[2,8] TKIs in combination with other agents (e.g., chemotherapy or corticosteroids) are recommended for induction therapy for Ph+ ALL. TKIs have also been incorporated into consolidation and maintenance therapy, as well as in the relapsed/refractory setting (category 2A). TKI options include: Bosulif® (bosutinib tablets), Sprycel® (dasatinib tablets), imatinib, Tasigna, or Iclusig® (ponatinib tablets) [category 2A]. NCCN panel notes that not all TKIs have been directly studied within the context of each specific regimen and there are limited data for Bosulif in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance and disease-related features. For adults and adolescents, Iclusig has activity against T315I mutations and/or in whom no other TKI is indicated (category 2A).
- **CML:** NCCN guidelines (version 2.2023 – April 13, 2023) recommend Tasigna as a preferred primary treatment for newly diagnosed chronic phase Ph+ CML patients with a low-, intermediate-, or high-risk score (category 1).[3,8] Tasigna is also recommended as an alternative TKI treatment (after primary treatment with imatinib, Bosulif® [bosutinib tablets], or Sprycel® [dasatinib tablets]) for BCR-ABL1 transcript levels (category 2A). Tasigna is also recommended in a variety of other situations, including post-allogeneic hematopoietic stem cell transplant (category 2A).
- **Gastrointestinal Stromal Tumor (GIST):** NCCN guidelines (version 1.2023 – March 13, 2023) recommend Tasigna as "useful in certain circumstances" after failure on approved therapies (category 2A).[4] Imatinib is a preferred regimen for first-line therapy (category 1) for sensitive mutations (excluding platelet-derived growth factor receptor alpha (*PDGFRA*) exon 18 mutations that are insensitive to imatinib including D842V mutation). Ayvakit® (avapritinib tablets) is also a preferred regimen (category 2A) for GIST with *PDGFRA* exon 18 mutations that are insensitive to imatinib, including the *PDGFRA* D842V mutation. Second-line therapies include sunitinib as "preferred" (category 1) and Sprycel as "other recommended regimen" (category 2A). Stivarga® (regorafenib tablets) is a "preferred" third-line therapy (category 1). Qinlock™ (ripretinib tablets) is a "preferred" fourth-line therapy (category 1).
- **Melanoma: Cutaneous**: NCCN guidelines (version 2.2023 – March 10, 2023) recommend Sprycel as "useful in certain circumstances" for metastatic or unresectable disease with an

activating *KIT* mutation as second-line or subsequent therapy for disease progression, intolerance, and/or projected risk of progression with *BRAF*-targeted therapy.[5]

- **Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions:** NCCN guidelines (version 1.2023 – May 19, 2023) recommend Tasigna as a preferred agent as "other recommended regimens" for *ABL1* rearrangements (category 2A).[6] It is also recommended as treatment in combination with ALL- or acute myeloid leukemia-type induction chemotherapy followed by allogeneic hematopoietic stem cell transplantation (HSCT) [if eligible] for lymphoid, myeloid or mixed lineage neoplasms with eosinophilia and *ABL1* rearrangement in blast phase (category 2A).[8]
- **Soft Tissue Sarcomas:** NCCN guidelines (version 2.2023 – April 25, 2023) recommend Tasigna as "useful in certain circumstances" as single-agent therapy for the treatment of pigmented villonodular synovitis/tenosynovial giant cell tumor (category 2A).[7] Turalio® (pexidartinib capsules) is the preferred regimen (category 1) and imatinib is also cited as "useful in certain circumstances" (category 2A).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tasigna. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tasigna is recommended in those who meet one of the following criteria:

FDA-Approved Indication

6. **Chronic Myeloid Leukemia.** Approve for 1 year if the patient has Philadelphia chromosome-positive chronic myeloid leukemia.

Other Uses with Supportive Evidence

7. **Acute Lymphoblastic Leukemia.** Approve for 1 year if the patient meets the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has Philadelphia chromosome-positive acute lymphoblastic leukemia.

8. **Gastrointestinal Stromal Tumor.** Approve for 1 year if the patient meets the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has tried each of the following (i, ii, iii, and iv):
      i. Imatinib or Ayvakit (avapritinib tablets); AND
      ii. Sunitinib or Sprycel (dasatinib tablets); AND
      iii. Stivarga (regorafenib tablets); AND
      iv. Qinlock (ripretinib tablets).

9. **Melanoma, Cutaneous.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
   I) Patient is ≥ 18 years of age; AND

J) Patient has metastatic or unresectable disease; AND
K) Patient has an activating *KIT* mutation; AND
L) Patient has tried at least one systemic regimen.
Note: Examples of a systemic regimen include: Opdivo (nivolumab intravenous infusion) + Yervoy (ipilimumab intravenous infusion), Opdivo + Opdualag (nivolumab/relatlimab-rmbw intravenous infusion), Keytruda (pembrolizumab intravenous infusion), Opdivo, Tafinlar (dabrafenib capsules) + Mekinist (trametinib tablets), Zelboraf (vemurafenib tablets) + Cotellic (cobimetinib tablets), Braftovi (encorafenib capsules) + Mektovi (binimetinib tablets).

10. Myeloid/Lymphoid Neoplasms with Eosinophilia. Approve for 1 year if the patient meets the following criteria (A and B):
H) Patient is ≥ 18 years of age; AND
I) The tumor has an *ABL1* rearrangement.

~~11.~~ Pigmented Villonodular Synovitis/Tenosynovial Giant Cell Tumor. Approve for 1 year if the patient meets one of the following criteria (A or B):
A) Patient has tried Turalio (pexidartinib capsules); OR
B) Patient cannot take Turalio, according to the prescriber.
Note: Examples of reasons for not being able to take Turalio include patients with elevated liver enzymes or concomitant use of medications that are associated with hepatotoxicity.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tasigna is not recommended in the following situations:

27. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

67. Tasigna® capsules [prescribing information]. East Hanover, NJ: Novartis; September 2021.
68. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 1.2022 – April 4, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 11, 2023.
69. The NCCN Chronic Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 2.2023 – April 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 10, 2023.
70. The NCCN Gastrointestinal Stromal Tumors Guidelines in Oncology (version 1.2023 – March 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 10, 2023.
71. The NCCN Melanoma: Cutaneous Clinical Practice Guidelines in Oncology (version 2.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 10, 2023.
72. The NCCN Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions Clinical Practice Guidelines in Oncology (version 1.2023 – May 19, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 10, 2023.
73. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 2.2023 – April 15, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 10, 2023.
74. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Search term: nilotinib. Accessed on May 10, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tazverik Prior Authorization Policy
- Tazverik® (tazemetostat tablets – Epizyme)

REVIEW DATE: 03/01/2023

OVERVIEW

Tazverik, an EZH2 inhibitor, is approved in the following conditions:[1]

- **Epithelioid sarcoma**, in patients ≥ 16 years of age with metastatic or locally advanced disease not eligible for complete resection.
- **Follicular lymphoma**, in the following situations:
  - Relapsed or refractory disease, in adults whose tumors are positive for an EZH2 mutation as detected by an approved test and who have received at least two prior systemic therapies.
  - Relapsed or refractory disease, in adults who have no satisfactory alternative treatment options.

These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Guidelines

Tazverik is addressed in the following guidelines from the National Comprehensive Cancer Network:

- **Epithelioid Sarcoma:** Guidelines for soft tissue sarcoma (version 2.2022 – May 17, 2022) recommend Tazverik as a "Preferred" therapy for treatment of metastatic or locally advanced epithelioid sarcoma not eligible for complete resection.[2] No other therapies are listed for this specific subtype of soft tissue sarcoma.
- **Follicular Lymphoma:** Guidelines for B-cell lymphomas (version 2.2023 – February 8, 2023) recommend Tazverik as a third-line and subsequent therapy for follicular lymphoma, irrespective of EZH2 mutation status.[3] Tazverik is an "Other Recommended" regimen in the second-line setting for a patient who is elderly or infirm, and if none of the other therapies are expected to be tolerable in the opinion of the treating physician.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tazverik. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tazverik is recommended in those who meet one of the following criteria:

FDA-Approved Indications

6. **Epithelioid Sarcoma.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** Patient is ≥ 16 years of age; AND
   - **B)** Patient has metastatic or locally advanced disease; AND
   - **C)** Patient is not eligible for complete resection.

7. **Follicular Lymphoma.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has relapsed or refractory disease; AND
   - **C)** Patient meets ONE of the following (i or ii):
     - **i.** Patient has tried at least two prior systemic therapies; OR
     - **ii.** According to the prescriber, there are no appropriate alternative therapies.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tazverik is not recommended in the following situations:

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

19. Tazverik® tablets [prescribing information]. Cambridge, MA: Epizyme; June 2020.
20. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (Version 2.2022 – May 17, 2022). © 2022 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org/. Accessed on February 26, 2023.
21. The NCCN B-Cell Lymphoma Clinical Practice Guidelines in Oncology (Version 2.2023 – February 8, 2023). © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org/. Accessed on February 26, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Temozolomide Capsules Prior Authorization Policy
- Temodar® (temozolomide capsules – Merck, generic)

REVIEW DATE: 10/11/2023

OVERVIEW

Temozolomide, an alkylating agent, is indicated in adults for the following uses:[1]

- **Anaplastic astrocytoma,**
  - Newly diagnosed as adjuvant treatment
  - Refractory
- **Glioblastoma**, newly diagnosed, concomitantly used with radiotherapy and then as maintenance therapy.

Guidelines

The National Comprehensive Cancer Network (NCCN) Compendium recommends use of temozolomide for the indications listed in the FDA-Approved Indications and Other Uses with Supportive Evidence sections.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of temozolomide capsules. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of temozolomide capsules is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Anaplastic Astrocytoma.** Approve for 1 year.

2. **Glioblastoma Multiforme.** Approve for 1 year.
   Note: This includes glioblastoma and grade IV astrocytoma.

Other Uses with Supportive Evidence

3. **Bone Cancer.** Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient has tried one chemotherapy regimen; AND
     Note: Examples of a chemotherapy regimen include one or more of the following products: vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide.
   - **B)** Patient has ONE of the following (i or ii):
     - **i.** Ewing sarcoma; OR
     - **ii.** Mesenchymal chondrosarcoma.

4. **Brain Metastases from Solid Tumors.** Approve for 1 year.

5. **Ependymoma, Intracranial or Spinal.** Approve for 1 year.

6. **Glioma, Other Types.** Approve for 1 year.
   Note: Examples of other types of gliomas include pediatric diffuse high-grade glioma, oligodendroglioma, low-grade glioma, and circumscribed glioma. For anaplastic astrocytoma and glioblastoma multiforme, refer to the respective criteria under the FDA-approved indications.

7. **Gliosarcoma.** Approve for 1 year.

8. **Medulloblastoma.** Approve for 1 year if the patient has tried one chemotherapy regimen.
   Note: Examples of a chemotherapy regimen include one or more of the following products: cisplatin, cyclophosphamide, vincristine, lomustine.

9. **Melanoma.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient has unresectable or metastatic melanoma; AND
   B) Patient has tried one systemic regimen.
      Note: Examples of a systemic regimen include one or more of the following medications: Keytruda (pembrolizumab intravenous infusion), Opdivo (nivolumab intravenous infusion), Yervoy (ipilimumab intravenous infusion), Tafinlar (dabrafenib capsule), Mekinist (trametinib tablet), Zelboraf (vemurafenib tablet), Cotellic (cobimetinib tablet), Braftovi (encorafenib capsule), Mektovi (binimetinib tablet).

10. **Mycosis Fungoides/Sézary Syndrome.** Approve for 1 year if the patient meets the following (A and B):
    A) Patient has tried one prior therapy; AND
       Note: Examples of a prior therapy include topical carmustine, topical corticosteroids, topical imiquimod, topical retinoids, Adcetris (brentuximab vedotin intravenous infusion), gemcitabine.
    B) Patient has central nervous system (CNS) involvement.

11. **Neuroendocrine Tumors.** Approve for 1 year if the patient meets ONE of the following (A, B, C, D, E, or F):
    A) Patient has carcinoid tumors or neuroendocrine tumor of gastrointestinal tract, lung or thymus; OR
    B) Patient has islet cell tumors or pancreatic neuroendocrine tumors; OR
    C) Patient has extrapulmonary poorly differentiated neuroendocrine carcinoma; OR
    D) Patient has large or small cell carcinoma; OR
    E) Patient has mixed neuroendocrine-non-neuroendocrine neoplasm; OR
    F) Patient has well differentiated grade 3 neuroendocrine tumor.

12. **Pheochromocytoma or Paragangliomas.** Approve for 1 year in patients with unresectable or metastatic disease.

13. **Primary Central Nervous System Lymphoma.** Approve for 1 year.

14. **Small Cell Lung Cancer.** Approve for 1 year if the patient has tried one systemic regimen.
    Note: Examples of systemic regimen include one or more of the following products: cisplatin, etoposide, carboplatin, Tecentriq (atezolizumab intravenous infusion), Imfinzi (durvalumab intravenous infusion), irinotecan.

15. **Soft Tissue Sarcomas.** Approve for 1 year if the patient meets ONE of the following (A or B):
    - **A)** Patient has advanced or metastatic disease; OR
    - **B)** Patient has ONE of the following diagnoses (i or ii):
        - **i.** Non-pleomorphic rhabdomyosarcoma; OR
        - **ii.** Solitary fibrous tumor.

16. **Uterine Sarcomas**. Approve for 1 year if the patient has tried a chemotherapy regimen.
    Note: Examples of a chemotherapy regimen include one or more of the following products: doxorubicin, docetaxel, epirubicin, gemcitabine, ifosfamine, dacarbazine, vinorelbine.

17. **Uveal Melanoma.** Approve for 1 year if the patient has unresectable or metastatic disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of temozolomide capsules is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tepmetko Prior Authorization Policy
- Tepmetko® (tepotinib tablets – EMD Serono)

REVIEW DATE: 02/01/2023

OVERVIEW

Tepmetko, a kinase inhibitor, is indicated for the treatment of adults with metastatic **non-small cell lung cancer (NSCLC)** harboring mesenchymal-epithelial transition (*MET*) exon 14 skipping alterations.[1] This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Guidelines

The National Comprehensive Cancer Network (NCCN) NSCLC guidelines (version 1.2023 – December 22, 2022) recommend Tepmetko as a first-line or subsequent line treatment option for patients with advanced or metastatic NSCLC who are positive for *MET* exon 14 skipping mutations or high-level *MET* amplification.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tepmetko. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tepmetko is recommended in those who meet the following criteria:

FDA-Approved Indication

12. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has advanced or metastatic disease; AND
- **C)** Patient meets one of the following criteria (i or ii):
- **i.** Patient has mesenchymal epithelial transition (*MET*) exon 14 skipping mutations as detected by an approved test; OR
- **ii.** Patient has high-level *MET* amplification as detected by an approved test.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tepmetko is not recommended in the following situations:

8. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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28. Tepmetko® tablets [prescribing information]. Rockland, MA: EMD Serono; February 2021.
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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Thalomid Prior Authorization Policy
- Thalomid® (thalidomide capsules – Celgene)

REVIEW DATE: 05/10/2023

OVERVIEW

Thalomid, an immunomodulatory agent, is indicated for the following uses:[1]

- **Erythema nodosum leprosum (ENL)**, acute treatment of cutaneous manifestations in moderate to severe disease. Thalomid is not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis.
- **ENL**, maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence.
- **Multiple myeloma**, newly diagnosed, in combination with dexamethasone.

Other Uses with Supportive Evidence

Discoid Lupus Erythematosus or Cutaneous Lupus Erythematosus

Thalomid has been used for discoid lupus erythematosus and cutaneous lupus erythematosus. Patients usually had refractory disease after trial of other therapies and good responses were achieved for many patients given Thalomid.[2-12] A retrospective medical review was done that involved 29 patients with refractory cutaneous manifestations of cutaneous lupus erythematosus who received Thalomid. Of the 23 patients who took Thalomid for 1 month, 74% of patients (n = 17/23) had complete resolution of the cutaneous manifestations and 13% of patients (n = 3/23) had a 75% or greater partial improvement.[3] Another report involving patients with discoid lupus (n = 18), subacute cutaneous lupus (n = 6), and systemic lupus erythematosus with skin involvement (n = 24) who had been resistant to at least two other treatments found a response rate of 81% (n = 39/48) with use of Thalomid with 60% of patients (n = 29/48) achieving a complete cutaneous remission.[4] Other therapies used for these conditions include antimalarial agents (e.g. hydroxychloroquine), corticosteroids (oral, topical, intralesional), methotrexate, azathioprine, cyclosporine, dapsone, mycophenolate mofetil, topical calcineurin inhibitors (e.g., Elidel® [pimecrolimus 1% cream], Protopic® [tacrolimus 0.03% and 0.1% ointment]), and Soriatane® (acitretin capsules).[2,7,12]

Prurigo Nodularis

Thalomid has been studied in patients with prurigo nodularis, most of whom were refractory to other treatments or with adverse events from the other therapies.[2,13-15] A retrospective review assessed the medical records of 42 patients with prurigo nodularis who were refractory to other therapy and who received Thalomid.[13] Patients received Thalomid for an average of 105 weeks. Previous therapies tried included topical steroids, intralesional steroids, systemic steroids, topical tar, macrolides, cyclosporine, azathioprine, methotrexate, calcineurnin inhibitors, antihistamines, dapsone, capsaicin, laser therapy, psoralen plus ultraviolet A therapy, ultraviolet B therapy, retinoids, hydroxyzine, and macrolides. With Thalomid, improvement was noted in approximately one-third of patients.

Aphthous Ulcers or Aphthous Stomatitis

Recurrent aphthous ulcers and recurrent aphthous stomatitis are associated with frequent and recurring symptoms that are painful and can lead to difficulty in speaking, eating, and swallowing.[16-27] Ulcers are larger and may persist for weeks to months. The conditions are noted in certain disease states such as in patients who are human immunodeficiency virus (HIV)-positive and Bechet's disease. In general, few adequately powered trials have assessed the efficacy of therapeutic agents for aphthous ulcers or aphthous

stomatitis. Although the data are older and limited, Thalomid has led to rapid resolution of symptoms in patients with recurrent aphthous ulcers or aphthous stomatitis.[16-27] A double-blind, randomized, placebo-controlled study assessed Thalomid as a therapy for oral aphthous ulcers in patients infected with HIV. In total, 55% of patients (n = 16/29) given Thalomid had complete healing of their aphthous ulcers after 4 weeks compared with only 7% of patients (n = 2/28) who received placebo. Patients given Thalomid had symptom improvements in regards to discomfort that occurred while eating.[21] A retrospective cohort study involving patients with recurrent aphthous stomatitis found that Thalomid was rapidly effective as 85% of patients (n = 78/92) achieved a complete remission of the condition within 14 days.[25] Many other agents have been used for recurrent aphthous ulcers or stomatitis including topical or intralesional corticosteroids, systemic corticosteroids, topical anesthetics/analgesics (lidocaine 2% viscous solution, benzocaine lozenges), antimicrobial mouth washes (tetracycline, chlorhexidine), topical sucralfate, acyclovir, pentoxifylline, dapsone, colchicine, and azathioprine.[16-27] Due to toxicities, use of Thalomid is generally reserved for patients who have not obtained satisfactory results with other agents.[26,27]

Guidelines

Thalomid is addressed in guidelines from National Comprehensive Cancer Network (NCCN):

- **Castleman's Disease:** The NCCN guidelines for B-cell lymphomas (version 2.2023 – February 8, 2023) recommend use of Thalomid, with or without rituximab, for patients with Castleman's disease for those who have relapsed/refractory or progressive disease (category 2A).[28] Thalomid is cited as an "other recommended therapy" (when given with cyclophosphamide and prednisone) for patients with multi-centric Castleman's disease who are negative for HIV and human herpesvirus-8 (HHV-8) [category 2A].
- **Histiocytic Neoplasms:** The NCCN guidelines for histiocytic neoplasms (version 1.2022 – May 20, 2022) recommend Thalomid in a few clinical scenarios.[29] For Langerhans cell histiocytosis, Thalomid is recommended as first-line or as subsequent therapy for single system multifocal skin disease (including mucosa) and for relapsed/refractory disease (category 2A). Thalomid is also recommended as first-line or subsequent therapy for cutaneous skin disease associated with Rosai-Dorfman disease under "useful in certain circumstances" (category 2A) [e.g., those with relapsed/refractory disease, symptomatic multifocal disease, symptomatic unresectable unifocal disease].
- **Kaposi Sarcoma:** The NCCN guidelines for Kaposi sarcoma (version 1.2023 – December 20, 2022) recommended Thalomid as an agent "useful under certain conditions" for subsequent systemic therapy options for relapsed/refractory therapy (category 2A) [for patients with corticosteroid-refractory immune reconstitution inflammatory syndrome].[30] This includes use when given alone (in patients without HIV) or with antiretroviral therapy for patients with HIV. First-line systemic therapy options include liposomal doxorubicin (preferred), and paclitaxel. Other subsequent systemic therapy options for relapsed/refractory therapy are also cited (e.g., Pomalyst® [pomalidomide capsules] {preferred}, lenalidomide, imatinib).
- **Multiple Myeloma:** The NCCN guidelines for multiple myeloma (version 3.2023 – December 8, 2022) recommend use of Thalomid in various scenarios (category 1 for use with bortezomib and dexamethasone; category 2A for others).[31] It is considered "useful in certain circumstances" among patients with previously treated multiple myeloma, as well as for primary therapy for transplant candidates. Thalomid is always recommended to be used with at least two other therapies to comprise the regimen.
- **Myelofibrosis:** The NCCN has guidelines regarding myeloproliferative neoplasms (version 3.2022 – August 11, 2022) discuss myelofibrosis.[32] Thalomid is recommended in the management of anemia associated with myelofibrosis "useful in certain circumstances", with or without prednisone, for a variety of clinical scenarios (category 2A) including patients with erythropoietin levels ≥ 500 mU/mL and with erythropoietin levels < 500 mU/mL and no response or loss of response to erythropoietic stimulating agents.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Thalomid. All approvals are provided for the duration noted below.

Automation: None.

Recommended Authorization Criteria
Coverage of Thalomid is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Erythema Nodosum Leprosum.** Approve for 1 year.

2. **Multiple Myeloma.** Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Thalomid is being taken in combination with at least two other medications.
     Note: Examples of medications include bortezomib, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, etoposide, and Kyprolis (carfilzomib intravenous infusion).

Other Uses with Supportive Evidence

3. **Castleman's Disease.** Approve for 1 year if the patient meets one of the following (A or B):
   - **A)** Patient has relapsed/refractory or progressive disease; OR
   - **B)** Patient meets the following criteria (i and ii):
     - **i.** Patient has multi-centric Castleman's disease; AND
     - **ii.** Patient is negative for the human immunodeficiency virus and human herpesvirus-8.

4. **Discoid Lupus Erythematosus or Cutaneous Lupus Erythematosus.** Approve for 1 year if the patient has tried at least two other medications.
   Note: Examples of medications include corticosteroids (oral, topical, intralesional), antimalarial agents (e.g., hydroxychloroquine), topical calcineurin inhibitors (e.g., Protopic [tacrolimus ointment], Elidel [pimecrolimus cream]), azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, dapsone, and Soriatane (acitretin capsules).

5. **Kaposi Sarcoma.** Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient has tried at least one medication; AND
     Note: Examples include liposomal doxorubicin, paclitaxel, Pomalyst (pomalidomide capsules), lenalidomide, and imatinib.
   - **B)** Patient has relapsed or refractory disease.

6. **Langerhans Cell Histiocytosis.** Approve for 1 year if the patient has multifocal skin disease.

7. **Myelofibrosis.** Approve for 1 year if the patient meets one of the following (A or B):
   - **C)** Patient meets the following criteria (i, ii, and iii):
     - **iv.** Patient is ≥ 18 years of age; AND
     - **v.** According to the prescriber the patient has anemia; AND
     - **vi.** Patient has serum erythropoietin levels ≥ 500 mU/mL; OR

D) Patient meets the following criteria (i, ii, iii, and iv):
- **v.** Patient is ≥ 18 years of age; AND
- **vi.** According to the prescriber the patient has anemia; AND
- **vii.** Patient has serum erythropoietin levels < 500 mU/mL; AND
- **viii.** Patient has experienced no response or loss of response to an erythropoiesis-stimulating agent.

8. **Prurigo Nodularis.** Approve for 1 year if the patient has tried at least two other medications.
   Note: Examples of medications include topical steroids, intralesional steroids, systemic steroids, topical tar, cyclosporine, macrolides, azathioprine, methotrexate, topical calcineurin inhibitors (Elidel [pimecrolimus cream], Protopic [tacrolimus ointment]), retinoids, antihistamines, hydroxyzine, dapsone, capsaicin, psoralen plus ultraviolet A therapy, and ultraviolet B therapy.

9. **Recurrent Aphthous Ulcers or Aphthous Stomatitis.** Approve for 1 year if the patient has tried at least two other medications.
   Note: Examples of medications include topical or intralesional corticosteroids, systemic corticosteroids, topical anesthetics/analgesics (e.g., lidocaine 2% viscous solution, benzocaine lozenges), antimicrobial mouthwashes (e.g., tetracycline, chlorhexidine), topical sucralfate, acyclovir, pentoxifylline, dapsone, colchicine, and azathioprine.

10. **Rosai-Dorfman Disease.** Approve for 1 year if the patient has cutaneous disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Thalomid is not recommend in the following situations:

28. **Cancer Cachexia.** Several small studies are available that have investigated Thalomid in the management of cancer cachexia related to various cancers.[33-37] A single center double-blind, controlled trial randomized patients with pancreatic cancer who had lost at least 10% of their body weight to receive Thalomid or placebo for 24 weeks (n = 50).[34] Of the 33 patients evaluable at 4 weeks, patients given Thalomid had gained an average of 0.37 kg compared with a loss of 2.21 kg in the patients given placebo.[34] A published review of data regarding use of Thalomid for the management of cancer cachexia concluded that there is inadequate evidence to recommend Thalomid in clinical practice.[37]

29. **Crohn's Disease.** Several publications report use of Thalomid in patients with Crohn's disease.[38-54] Thalomid was used as an adjunctive therapy, or in those refractory to other therapy, and usually involved children. The data were not of high quality and primarily consisted of open-label designs or retrospective reviews, without a placebo control, and involved very few patients.[38-54] Guidelines from the American College of Gastroenterology (2018) for the management of Crohn's disease in adults do not mention Thalomid as a therapeutic alternative.[49] Also, guidelines from the American Gastroenterological Association (2021) do not mention Thalomid in the guidelines for the medical management of moderate to severe luminal and perianal fistulizing Crohn's Disease.[55] Although some improvements were noted in published data with Thalomid, more definite data from randomized, controlled trials are required before this is a recommended therapy.[49] Consensus guidelines of the European Crohn's and Colitis Organization and the European society of Pediatric Gastroenterology, Hepatology and Nutrition (2014) state that even though some data are available that suggest efficacy of Thalomid in refractory pediatric Crohn's disease, there are insufficient data to recommended Thalomid therapy at this juncture.[54] Many other therapies are available for the management of Crohn's disease.

30. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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51. Yang C, Singh P, Singh H, et al. Systematic review: thalidomide and thalidomide analogues for treatment of inflammatory bowel disease. *Aliment Pharmacol Ther*. 2015;41:1079-1093.
52. Bramuzzo M, Ventura A, Martelossi S, Lazzerini M. Thalidomide for inflammatory bowel disease. Systematic review. *Medicine (Baltimore)*. 2016;95(30):e4239.
53. Kammermeier J, Morris MA, Garrick V, et al, for the BSPGHAN IBD Working Group. Management of Crohn's disease. *Arch Dis Child*. 2016;101:475-480.
54. Ruemmele FM, Veres G, Volho KL, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. *J Crohns Colitis*. 2014;8(10):1179-1207.
55. Feuerstein JD, Ho EY, Shmidt E, et al. AGA Clinical Practice Guidelines on the medical management of moderate to severe luminal and perianal fistulizing Crohn's Disease. *Gastroenterology*. 2021;160(7):2496-2508.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tibsovo Prior Authorization Policy
- Tibsovo® (ivosidenib tablets –Servier/Les)

REVIEW DATE: 03/08/2023; selected revision 04/19/2023 and 11/01/2023

OVERVIEW

Tibsovo, an isocitrate dehydrogenase-1 (IDH1) inhibitor, is indicated for the treatment of cancers with a susceptible *IDH1* mutation as detected by an FDA-approved test:[1]

- **Acute myeloid leukemia, newly diagnosed disease, in combination with azacitidine or as monotherapy,** in patients who are ≥ 75 years of age or who have comorbidities that preclude use of intensive induction chemotherapy.
- **Acute myeloid leukemia, relapsed or refractory disease**, in adults.
- **Cholangiocarcinoma, locally advanced or metastatic**, in adults who have been previously treated.
- **Myelodysplastic syndrome, relapsed or refractory disease**, in adults.

Guidelines

Tibsovo is discussed in the National Comprehensive Cancer Network (NCCN) guidelines:[2]

- **Acute Myeloid Leukemia:** NCCN guidelines (version 1.2023 – March 3, 2023) recommend Tibsovo as a single-agent (category 2A) or in combination with azacitidine (category 1) as "Preferred" therapy for treatment induction for patients with an *IDH1* mutation who are not candidates for intensive induction therapy; and it is also used for follow-up after induction therapy, and consolidation therapy for patients with an *IDH1* mutation. Tibsovo is also recommended for relapsed or refractory disease with *IDH1* mutation (category 2A).[3]
- **Bone Cancer:** NCCN guidelines (version 2.2023 – September 28, 2022) recommend Tibsovo for conventional (grades 1 to 3) and dedifferentiated chondrosarcoma in patients with susceptible *IDH1* mutations as "Useful in Certain Circumstances" (category 2A).[5]
- **Central Nervous System Cancers:** NCCN guidelines (version 1.2023 – March 24, 2023) recommend Tibsovo for recurrent or progressive *IDH-1* mutant oligodendroglioma World Health Organization (WHO) grade 2 as "other recommend regimens" and WHO grade 3 as "useful in certain circumstances" (both category 2A) and *IDH-1* mutant astrocytoma WHO grade 2 as "other recommend regimens" (category 2A) and WHO grade 3 or 4 as "useful in certain circumstances" (category 2B).[6]
- **Cholangiocarcinoma:** NCCN guidelines for hepatobiliary cancers (version 5.2022 – January 13, 2023) cite Tibsovo as "Useful in Certain Circumstances" for patients with cholangiocarcinoma with *IDH1* mutations as subsequent-line therapy if there is disease progression (category 2A).[4]
- **Myelodysplastic Syndromes:** NCCN guidelines (version 2.2023 – October 17, 2023) state that emerging data are demonstrating effectiveness of Tibsovo and Idhifa® (enasidenib) for patients with myelodysplastic syndrome with *IDH* 1 or *IDH* 2 mutations.[7]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tibsovo. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tibsovo is recommended in those who meet one of the following criteria:

FDA-Approved Indications

5. **Acute Myeloid Leukemia.** Approve for 1 year if the patient meets the following (A and B):
   - **D)** Patient is ≥ 18 years of age; AND
   - **E)** Patient has isocitrate dehydrogenase-1 (*IDH1*) mutation-positive disease as detected by an approved test.

6. **Cholangiocarcinoma.** Approve for 1 year if the patient meets the following (A, B and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has isocitrate dehydrogenase-1 (*IDH1*) mutation-positive disease; AND
   - **C)** Patient has been previously treated with at least one chemotherapy regimen.
     Note: Examples are gemcitabine + cisplatin; Imfinzi (durvalumab intravenous infusion) + gemcitabine + cisplatin, 5-fluorouracil + oxaliplatin or cisplatin; capecitabine + oxaliplatin or cisplatin; gemcitabine + Abraxane (paclitaxel protein-bound particles intravenous infusion) or capecitabine or oxaliplatin; and FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin).

7. **Myelodysplastic Syndrome.** Approve for 1 year if the patient meets the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has isocitrate dehydrogenase-1 (*IDH1*) mutation-positive disease; AND
   - **C)** Patient has relapsed or refractory disease.

Other Uses with Supportive Evidence

8. **Bone Cancer.** Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient has chondrosarcoma; AND
   - **B)** Patient has isocitrate dehydrogenase-1 (*IDH1*) mutation-positive disease.

9. **Central Nervous System Cancer**. Approve for 1 year if the patient meets the following (A, B and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has recurrent or progressive disease; AND
   - **C)** Patient has meets one of the following (i or ii):
     - **i.** Patient has World Health Organization (WHO) grade 2 or 3 oligodendroglioma; OR
     - **ii.** Patient has WHO grade 2 astrocytoma.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tibsovo is not recommended in the following situations:

31. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

17. Tibsovo® tablets [prescribing information]. Boston, MA: Servier; October 2023.
18. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 12, 2023. Search term: ivosidenib.

19. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 1.2023 – March 3, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 7, 2023.
20. The NCCN Hepatobiliary Cancers Clinical Practice Guidelines in Oncology (version 5.2022 – January 13, 2023). © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 7, 2023.
21. The NCCN Bone Cancers Clinical Practice Guidelines in Oncology (version 2.2023 – September 28, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 7, 2023.
22. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 1.2023 – March 24, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 12, 2023.
23. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 2.2023 – October 17, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 27, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Truqap Prior Authorization Policy
- Truqap™ (capivasertib tablets – AstraZeneca)

REVIEW DATE: 11/29/2023; selected revision 01/03/2024

OVERVIEW

Truqap, a kinase inhibitor, is indicated in combination with fulvestrant for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with one or more phosphatidylinositol 3-kinase (*PIK3CA*)/ serine/threonine protein kinase 1 (*AKT1*)/ phosphatase and tensin homolog (*PTEN*)-alterations as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy in adults.[1]

Guidelines

National Comprehensive Cancer Network (NCCN) breast cancer guidelines (version 5.2023 – December 5, 2023) state that for patients with HR+/HER2-negative tumors with *PIK3CA/AKT1/PTEN*-activating mutations, Truqap + fulvestrant is a "Preferred Regimen" for second or subsequent-line therapy in selected patients (category 1).[2] This would include adults with *PIK3CA/AKT1/PTEN*-activating mutations after disease progression or recurrence after one or more prior lines of endocrine therapy, including one line containing a cyclin-dependent kinase (CDK) 4/6 inhibitor. In this setting, for patients with PIK3CA-mutated tumors, Piqray® (alpelisib tablets) + fulvestrant is recommended (category 1). In the first-line setting for all patients, aromatase inhibitor or fulvestrant is recommended in combination with a CDK4/6 inhibitor (category 1 or category 2A).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Truqap. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Truqap is recommended in those who meet the following criteria:

FDA-Approved Indication

8. Breast Cancer. Approve for 1 year if the patient meets the following (A, B, C, D, E, and F):
- **R)** Patient is ≥ 18 years of age; AND
- **S)** Patient has locally advanced or metastatic disease; AND
- **T)** Patient has hormone receptor-positive (HR+) disease; AND
- **U)** Patient has human epidermal growth factor receptor 2 (*HER2*)-negative disease; AND
- **V)** Patient has at least one phosphatidylinositol 3-kinase (*PIK3CA*), serine/threonine protein kinase (*AKT1*), or phosphatase and tensin homolog (*PTEN*)-alteration; AND
- **W)** Patient meets one of the following (i or ii):
  - **i.** Patient meets both of the following (a and b):

a) Patient has had progression with at least one endocrine-based regimen in the metastatic setting; AND
Note: Examples of endocrine-based therapy include anastrozole, exemestane, and letrozole.

b) Patient has had progression with at least one cyclin-dependent kinase (CDK) 4/6 inhibitor in the metastatic setting; OR
Note: Examples of CDK4/6 inhibitor include: Ibrance (palbociclib tablets or capsules), Verzenio (abemaciclib tablets), Kisqali (ribociclib tablets), Kisqali Femara Co-Pack (ribociclib and letrozole tablets).

ii. Patient has recurrence on or within 12 months of completing adjuvant endocrine therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Truqap is not recommended in the following situations:

8. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

22. Truqap™ tablets [prescribing information]. Wilmington, DE: AstraZeneca; November 2023.
23. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 5.2023 –December 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 3, 2024.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Truseltiq Prior Authorization Policy
- Truseltiq™ (infigratinib capsules – QED Therapeutics)

REVIEW DATE: 06/14/2023

OVERVIEW

Truseltiq, a kinase inhibitor, is indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic **cholangiocarcinoma** with a fibroblast growth factor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test.[1] This indication was approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

In October 2022, Helsinn, the manufacturer, announced the discontinuation of distribution of Truseltiq on March 31, 2023.[4] Helsinn stated that this was not for safety reason and they recommend that no new patients be started on Truseltiq.

Guidelines

The National Comprehensive Cancer Network Hepatobiliary Cancers (version 2.2023 – May 10, 2023) clinical practice guidelines no longer recommend Truseltiq for the subsequent treatment of unresectable or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements, as a single agent for progression on or after systemic treatment.[2,3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Truseltiq. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Truseltiq is recommended in those who meet the following criteria:

FDA-Approved Indication

9. Cholangiocarcinoma. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
- **A)** Patient is currently receiving Truseltiq; AND
- **B)** Patient is ≥ 18 years of age; AND
- **C)** Patient has unresectable locally advanced or metastatic disease; AND
- **D)** Patient has fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement, as detected by an approved test; AND
- **E)** Truseltiq is used as subsequent therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Truseltiq is not recommended in the following situations:

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

24. Truseltiq™ capsules [prescribing information]. Brisbane, CA: QED Therapeutics; May 2021.
25. The NCCN Hepatobiliary Cancers Clinical Practice Guidelines in Oncology (version 2.2023 – May 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 12, 2023.
26. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 12, 2023. Search term: infigratinib.
27. Important information: Truseltiq® (infigratinib) capsules notice of permanent discontinuation of distribution [press release]. Iselin, NJ: Helsinn Therapeutics; October 2022. Available at: https://www.ccanewsonline.com/web-exclusives/press-releases/october-10-2022-truseltiq. Accessed on June 12, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tukysa Prior Authorization Policy
- Tukysa® (tucatinib tablets –Seagan)

REVIEW DATE: 06/07/2023

OVERVIEW

Tukysa, a kinase inhibitor, is indicated for the following uses:[1]

- **Breast cancer**, in combination with trastuzumab and capecitabine, for the treatment of advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive disease, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting in adults.
- **Colorectal cancer**, in combination with trastuzumab, for the treatment of RAS wild-type HER2-positive unresectable or metastatic disease that has progressed following treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy in adults.
  This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Guidelines

Tukysa is discussed in the guidelines from the National Comprehensive Cancer Network (NCCN):

- **Breast Cancer:** NCCN guidelines (version 4.2023 – March 23, 2023) recommend Tukysa + trastuzumab + capecitabine in the third-line and beyond setting as a "preferred regimen" (category 1) for the treatment of recurrent unresectable (local or regional) or Stage IV HER2-positive disease in patients with both systemic and central nervous system (CNS) progression.[2] There is a footnote that states it may be given in the second-line setting. Perjeta® (pertuzumab intravenous infusion) + trastuzumab + docetaxel (category 1) and Perjeta + trastuzumab + paclitaxel (category 2A) are recommended first-line regimens. Enhertu® (fam-trastuzumab deruxtecan-nxki intravenous infusion) [category 1] is a recommended second-line agent.
- **Colon Cancer and Rectal Cancer:** NCCN colon cancer guidelines (version 2.2023 – April 25, 2023) and NCCN rectal cancer guidelines (version 3.2023 – May 26, 2023) recommend Tukysa in combination with trastuzumab as a primary or subsequent treatment option for advanced or metastatic HER2-amplified, *RAS* and *BRAF* wild type disease (category 2A) in a variety of different clinical scenarios.[3,4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tukysa. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tukysa is recommended in those who meet one of the following criteria:

FDA-Approved Indications

13. Breast Cancer. Approve for 1 year if the patient meets ALL of the criteria (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has recurrent or metastatic breast cancer; AND
- **C)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **D)** Patient has received at least one prior anti-HER2-based regimen in the metastatic setting; AND
  Note: Examples of anti-HER2-based regimens include Perjeta (pertuzumab intravenous infusion) + trastuzumab + docetaxel, Perjeta + trastuzumab + paclitaxel; Kadcyla (ado-trastuzumab emtansine intravenous infusion), capecitabine + trastuzumab or lapatinib tablets, trastuzumab + lapatinib tablets, Enhertu (fam-trastuzumab deruxtecan-nxki intravenous infusion), trastuzumab + docetaxel or vinorelbine, Nerlynx (neratinib tablets) + capecitabine, and Margenza (margetuximab-cmkb intravenous infusion) + chemotherapy (capecitabine, Halaven [eribulin intravenous infusion], gemcitabine, or vinorelbine).
- **E)** The medication is used in combination with trastuzumab and capecitabine.

14. Colon and Rectal Cancer. Approve for 1 year if the patient meets ALL of the criteria (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has unresectable or metastatic disease; AND
- **C)** Patient has human epidermal growth factor receptor 2 (HER2)-amplified disease; AND
- **D)** Patient's tumor or metastases are wild-type *RAS* (*KRAS* wild-type and *NRAS* wild-type); AND
- **E)** The medication is used in combination with trastuzumab.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tukysa is not recommended in the following situations:

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

30. Tukysa® tablets [prescribing information]. Bothell, WA: Seagen; January 2023.
31. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – March 23, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 2, 2023.
32. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 6, 2023.
33. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – May 26, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 6, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Turalio Prior Authorization Policy
- Turalio® (pexidartinib capsules – Daiichi Sankyo)

REVIEW DATE: 08/30/2023

OVERVIEW

Turalio, a kinase inhibitor, is indicated for the treatment of **symptomatic tenosynovial giant cell tumor** associated with severe morbidity or functional limitations and not amenable to improvement with surgery in adults.[1]

Guidelines

Turalio is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):

- **Histiocytic Neoplasms**: NCCN guidelines (version 1.2023 – August 11, 2023) recommend Turalio as first-line or subsequent therapy for *CSF1R* mutation target as "Useful in Certain Circumstances", for Langerhans cell histiocytosis, Erdheim-Chester disease, and Rosai-Dorfman disease in various settings (category 2A).[2-3]
- **Soft Tissue Sarcoma:** NCCN guidelines (version 2.2023 – April 25, 2023), indicate that Turalio is the "preferred" single-agent therapy for the treatment of pigmented villonodular synovitis/tenosynovial giant cell tumor (category 1).[3-4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Turalio. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Turalio is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1) **Tenosynovial Giant Cell Tumor (Pigmented Villonodular Synovitis).** Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** According to the prescriber, the tumor is not amenable to improvement with surgery.

Other Uses with Supportive Evidence

2) **Histiocytic Neoplasms.** Approve for 1 year if the patient meets the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has a colony stimulating factor 1 receptor (*CSF1R*) mutation; AND
   - **C)** Patient has one of the following (i, ii, or iii):

i. Langerhans cell histiocytosis; OR
ii. Erdheim-Chester disease; OR
iii. Rosai-Dorfman disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Turalio is not recommended in the following situations:

32. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

24. Turalio® capsules [prescribing information]. Basking Ridge, NJ: Daiichi Sankyo; October 2022.
25. The NCCN Histiocytic Neoplasms Clinical Practice Guidelines in Oncology (version 1.2023 – August 11, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed August 24, 2023.
26. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed August 24, 2023. Search term: pexidartinib.
27. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed August 24, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Valchlor Prior Authorization Policy
- Valchlor® (mechlorethamine topical gel – Helsinn)

REVIEW DATE: 12/13/2023

OVERVIEW

Valchlor, a nitrogen mustard, is indicated for the topical treatment of Stage IA and IB **mycosis fungoides-type cutaneous T-cell lymphoma** in patients who have received prior skin-directed therapy.[1]

Guidelines

Valchlor is addressed in National Comprehensive Cancer Network guidelines:

- **Histiocytic neoplasms:** Guidelines (version 1.2023 – August 11, 2023) recommend Valchlor for the topical treatment of unifocal Langerhans cell histiocytosis with isolated skin disease.[2,5]
- **Primary cutaneous lymphomas:** Guidelines (version 1.2023 – January 5, 2023) recommend Valchlor for the topical treatment of primary cutaneous B-cell lymphoma, mycosis fungoides/Sezary syndrome, and primary cutaneous CD30+ T-cell lymphoproliferative disorders.[2,3]
- **T-cell lymphomas:** Guidelines (version 1.2023 – January 5, 2023) recommend Valchlor for the topical treatment of adult T-cell leukemia/lymphoma – chronic/smoldering subtype.[2,4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Valchlor. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Valchlor is recommended in those who meet one of the following criteria:

FDA-Approved Indication

10. **Cutaneous Lymphomas**. Approve for 1 year if the patient is ≥ 18 years of age.
    Note: Includes mycosis fungoides/Sezary syndrome, primary cutaneous B-cell lymphoma, primary cutaneous CD30+ T-cell lymphoproliferative disorders.

Other Uses with Supportive Evidence

11. **Adult T-Cell Leukemia/Lymphoma**. Approve for 1 year if the patient has chronic/smoldering subtype of adult T-cell leukemia/lymphoma.

12. **Langerhans Cell Histiocytosis**. Approve for 1 year if, according to the prescriber, patient has unifocal Langerhans cell histiocytosis with isolated skin disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Valchlor is not recommended in the following situations:

10. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

28. Valchlor® topical gel [prescribing information]. Iselin, NJ: Helsinn; January 2020.
29. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 8, 2023. Search term: mechlorethamine.
30. The NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 8, 2023.
31. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 8, 2023.
32. The NCCN Histiocytic Neoplasms Clinical Practice Guidelines in Oncology (version 1.2023 – August 11, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed December 8, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Vanflyta Prior Authorization Policy
- Vanflyta® (quizartinib tablets – Daiichi Sankyo)

REVIEW DATE: 08/02/2023; selected revision 08/09/2023

OVERVIEW

Vanflyta, a kinase inhibitor, is indicated in combination with standard cytarabine and anthracycline induction and cytarabine consolidation, and as maintenance monotherapy following consolidation chemotherapy, for the treatment of **newly diagnosed acute myeloid leukemia (AML)** that is FMS-like tyrosine kinase 3 internal tandem duplication (**FLT3-ITD)-positive** as detected by an FDA-approved test in adults.[1]

Limitation of use: Vanflyta is not indicated as maintenance monotherapy following allogeneic hematopoietic stem cell transplantation (HSCT) and improvement in overall survival with Vanflyta in this setting has not been demonstrated.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for AML (version 4.2023 – July 11, 2023) do not address Vanflyta.[2] The guidelines recommend Rydapt® (midostaurin capsules) in several settings in adults with *FLT3*-mutated AML. Rydapt + chemotherapy is recommended for induction for newly diagnosed *FLT3-ITD/TKD* mutation-positive AML and for consolidation therapy (category 2A). Other consolidation therapies include hematopoietic cell transplantation (HCT), high dose cytarabine, or other chemotherapy. For maintenance therapy in patients with *FLT3-ITD* mutation who are in remission, sorafenib (category 2A), Rydapt (category 2B), and Xospata® (gilteritinib tablets) [category 2B] are recommended. For relapsed or refractory AML, Xospata is recommended for patients with *FLT3-ITD/TKD* mutations.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vanflyta. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vanflyta is recommended in those who meet the following criteria:

FDA-Approved Indication

10. Acute Myeloid Leukemia. Approve for 1 year if the patient meets the following (A, B and C):
- **C)** Patient is ≥ 18 years of age; AND
- **D)** Patient has *FLT3-ITD* mutation-positive disease as detected by an approved test; AND
- **E)** This medication is being used for induction, consolidation, or maintenance treatment.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vanflyta is not recommended in the following situations:

33. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

28. Vanflyta® tablets [prescribing information]. Basking Ridge, NJ: Daiichi Sankyo, July 2023.
29. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 4.2023 – July 11, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 28, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Venclexta Prior Authorization Policy
- Venclexta® (venetoclax tablets – AbbVie and Genentech)

REVIEW DATE: 07/19/2023

OVERVIEW

Venclexta, a B-cell lymphoma-2 inhibitor, is indicated in adults for the following uses:[1]

- **Acute myeloid leukemia (AML)**, in combination with azacitidine or decitabine or low-dose cytarabine for newly diagnosed AML in patients ≥ 75 years of age or who have comorbidities that preclude use of intensive induction chemotherapy.
- **Chronic lymphocytic leukemia (CLL)**.
- **Small lymphocytic lymphoma (SLL)**.

Guidelines

Venclexta is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):

- **AML**: NCCN guidelines (version 4.2023 – July 11, 2023) recommend Venclexta (in combination with decitabine, azacitidine or low-dose cytarabine) in a variety of clinical scenarios, such as induction therapy, post induction therapy, and relapsed or refractory disease. The guidelines recommend Venclexta (in combination with decitabine, azacitidine, or low-dose cytarabine) (category 2A) for Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) for systemic disease treated with palliative intent (patients with low performance and/or nutritional status) or relapsed/refractory disease.
- **B-Cell Lymphomas**: NCCN guidelines (version 5.2023 – July 7, 2023) address mantle cell lymphoma.[3] The guidelines cite Venclexta (continuous) ± rituximab (category 2A), Venclexta + Imbruvica® (ibrutinib tablets, capsules, and oral solution) [category 2A] as second-line therapy regimens as "useful in certain circumstances".
- **CLL/SLL**: NCCN guidelines (version 3.2023 – June 12, 2023) cite Venclexta in several scenarios.[4] For patients without 17p deletion/TP53 mutation, Venclexta + Gazyva® (obinutuzumab intravenous infusion) is listed as a "preferred" first-line therapy (category 1); Venclexta + rituximab is listed as a "preferred regimen" (category 1) and single-agent Venclexta is listed as "other recommended regimen" (category 2A) for second-line or third-line therapy.[3] For patients with 17p deletion/TP53 mutation, Venclexta + Gazyva is recommended as a "preferred regimen" first-line (category 2A); Venclexta + rituximab (category 1) and single-agent Venclexta (category 2A) are preferred second-line and subsequent therapy in this population. Many other first-line options are recommended. CLL and SLL are different manifestations of the same disease which are managed similarly.
- **Multiple Myeloma:** NCCN guidelines (version 3.2023 – December 8, 2022) recommend Venclexta + dexamethasone for previously treated multiple myeloma for relapse or progressive disease for patients with t (11;14) translocation as "useful in certain circumstances for early relapses (1-3 prior therapies) [category 2A].[5]
- **Systemic Light Chain Amyloidosis:** NCCN guidelines (version 2.2023 – November 28, 2022) list Venclexta ± dexamethasone as a therapy for previously treated disease for patients with t (11;14) translocation as "useful in certain circumstances" (category 2A).[6]
- **Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma:** NCCN guidelines (version 1.2023 – July 6, 2022) recommend single-agent Venclexta as "other recommended regimen" for previously treated disease (category 2A).[4-5]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Venclexta. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Venclexta is recommended in those who meet one of the following criteria:

FDA-Approved Indications

11. Acute Myeloid Leukemia. Approve for 1 year if the patient meets the following (A and B):
Note: Acute Myeloid Leukemia includes Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN).
A) Patient is ≥ 18 years of age; AND
B) Venclexta is used in combination with either azacitidine, decitabine, or cytarabine.

12. Chronic Lymphocytic Leukemia. Approve for 1 year if the patient is ≥ 18 years of age.

13. Small Lymphocytic Lymphoma. Approve for 1 year if the patient is ≥ 18 years of age.

Other Uses with Supportive Evidence

14. Mantle Cell Lymphoma. Approve for 1 year if the patient meets the following (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient has tried at least one systemic regimen.
Note: Examples of systemic regimens include those containing one or more of the following products: Imbruvica (ibrutinib tablets, capsules, and oral solution), rituximab, Calquence (acalabrutinib tablets), lenalidomide, dexamethasone, cytarabine, cisplatin, cyclophosphamide, doxorubicin, vincristine, high-dose methotrexate, cytarabine, or Treanda (bendamustine intravenous infusion).

15. Multiple Myeloma. Approve for 1 year if the patient meets the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has t (11;14) translocation; AND
C) Patient has tried at least one systemic regimen for multiple myeloma; AND
Note: Examples of systemic regimens include those containing one or more of the following products: bortezomib, Kyprolis (carfilzomib intravenous injection), lenalidomide, cyclophosphamide, or Ninlaro (ixazomib capsules).
D) Venclexta is used in combination with dexamethasone.

16. Systemic Light Chain Amyloidosis. Approve for 1 year if the patient meets the following (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patient has t (11;14) translocation; AND
C) Patient has tried at least one systemic regimen.
Note: Examples of systemic regimens include those containing one or more of the following products: bortezomib, lenalidomide, cyclophosphamide, and melphalan.

17. Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma. Approve for 1 year if the patient meets the following (A and B):

A) Patient is ≥ 18 years of age; AND

B) Patient has tried at least one systemic regimen.

Note: Examples of a systemic regimen contain one or more of the following products: Brukinsa (zanubrutinib capsules), Imbruvica (ibrutinib tablets, capsules, and oral solution), rituximab, bendamustine, cyclophosphamide, dexamethasone, bortezomib, fludarabine, or cladribine.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Venclexta is not recommended in the following situations:

34. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

75. Venclexta® tablets [prescribing information]. North Chicago, IL and South San Francisco, CA: AbbVie and Genentech; June 2022.
76. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 4.2023 – July 11, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 14, 2023.
77. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 5.2023 – July 7, 2023). © 2023 National Comprehensive Cancer Network. Available at http://www.nccn.org. Accessed on July 14, 2023.
78. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (version 3.2023 – June 12, 2023). © 2023 National Comprehensive Cancer Network. Available at http://www.nccn.org. Accessed on July 14, 2023.
79. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 3.2023 – December 8, 2022). © 2022 National Comprehensive Cancer Network. Available at http://www.nccn.org. Accessed on July 14, 2023.
80. The NCCN Systemic Light Chain Amyloidosis Clinical Practice Guidelines in Oncology (version 2.2023 – November 28, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 14, 2023.
81. The NCCN Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma Clinical Practice Guidelines in Oncology (version 1.2023 – July 6, 2022). © 2022 National Comprehensive Cancer Network. Available at http://www.nccn.org. Accessed on July 14, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Verzenio Prior Authorization Policy
- Verzenio® (abemaciclib tablets – Eli Lilly)

REVIEW DATE: 02/22/2023

OVERVIEW

Verzenio, a cyclin-dependent kinase (CDK) 4/6 inhibitor, is indicated for the treatment of hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative **breast cancer** in adults in the following settings:[1]

- **Early breast cancer**, in combination with endocrine therapy (tamoxifen or an aromatase inhibitor [AI]) for adjuvant treatment for node-positive disease at high risk of recurrence.
- **Advanced or metastatic breast cancer:**
  - In combination with an AI as initial endocrine-based therapy.
  - In combination with fulvestrant for disease progression following endocrine therapy.
  - As monotherapy for disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on **breast cancer** (version 2.2023 – February 7, 2023) recommend Verzenio with AI (category 2A) or fulvestrant (category 1) as a first-line "Preferred Regimen" for recurrent unresectable (local or regional) or Stage IV HR+ and HER2-negative disease in postmenopausal women or premenopausal patient receiving ovarian ablation or suppression.[2,3] The guidelines state in a footnote that in phase III randomized controlled trials, Kisqali® (ribociclib tablets) + endocrine therapy has shown overall survival benefit in the first-line setting. CDK4/6 inhibitor + fulvestrant is recommended for second- and subsequent-line therapy, if CDK4/6 inhibitor was not previously used (category 1) in this setting, which is a "Preferred Regimen". The guidelines state in a footnote that in phase III randomized controlled trials, fulvestrant in combination with a CDK4/6 inhibitor has shown overall survival benefit in the second-line setting. In this setting, single-agent Verzenio is recommended as a "Useful In Certain Circumstances" therapy (for subsequent treatment) if there is progression on prior endocrine therapy and prior chemotherapy in the metastatic setting (category 2A). For men with breast cancer, the compendium recommends they be treated similarly to postmenopausal women, except that the use of an aromatase inhibitor is ineffective without concomitant suppression of testicular steroidogenesis.[3] The guidelines also recommend Verzenio for 2 years as adjuvant therapy in combination with endocrine therapy in patients with HR+, HER2-negative, high risk (i.e., ≥4 positive lymph nodes, or 1-3 positive lymph nodes with one or more of the following: grade 3 disease, tumor size ≥5 cm, or a Ki-67 score of ≥20%) disease (category 2A).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Verzenio. All approvals are provided for duration noted below. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: a woman is defined as an individual with the biological traits of a woman, regardless of the individual's gender identity or gender expression; men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Verzenio is recommended in those who meet one of the following criteria:

FDA-Approved Indications

18. Breast Cancer - Early. Approve for 2 years if the patient meets the following criteria (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND
- **C)** Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
- **D)** Patient has node-positive disease at high risk of recurrence; AND
  Note: High risk includes patients with ≥4 positive lymph nodes, or 1-3 positive lymph nodes with one or more of the following: grade 3 disease, tumor size ≥5 cm, or a Ki-67 score of ≥20%.
- **E)** Patient meets ONE of the following criteria (i or ii):
  - **i.** Verzenio will be used in combination with anastrozole, exemestane, or letrozole AND patient meets one of the following (a ,b, or c):
    - **a)** Patient is a postmenopausal woman*; OR
    - **b)** Patient is a pre/perimenopausual woman* and meets one of the following [(1) or (2)]:
      - **(1)** Patient is receiving ovarian suppression/ablation with a gonadotropin-releasing hormone (GnRH) agonist; OR
        Note: Examples of a GnRH agonist include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous injection).
      - **(2)** Patient has had surgical bilateral oophorectomy or ovarian irradiation; OR
    - **c)** Patient is a man* and patient is receiving a gonadotropin-releasing hormone (GnRH) analog; OR
      Note: Examples of a GnRH analog include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous injection), Firmagon (degarelix acetate subcutaneous injection), Orgovyx (relugolix tablet).
  - **ii.** Verzenio will be used in combination with tamoxifen AND patient meets one of the following (a or b):
    - **a)** Patient is a postmenopausal woman* or man*; OR
    - **b)** Patient is a pre/perimenopausual woman* and meets one of the following [(1) or (2)]:
      - **(1)** Patient is receiving ovarian suppression/ablation with a gonadotropin-releasing hormone (GnRH) agonist; OR
        Note: Examples of a GnRH agonist include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous injection).
      - **(2)** Patient has had surgical bilateral oophorectomy or ovarian irradiation.

***** Refer to the Policy Statement.

19. Breast Cancer – Recurrent or Metastatic in Women*. Approve for 1 year if the patient meets the following criteria (A, B, C, D, E, and F):
- **X)** Patient is ≥ 18 years of age; AND

Y) Patient has recurrent or metastatic breast cancer; AND

Z) Patient has hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND

AA) Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND

BB) Patient meets ONE of the following criteria (i or ii):

- **i.** Patient is postmenopausal OR
- **ii.** Patient is pre/perimenopausal and meets one of the following (a or b):
  - **a)** Patient is receiving ovarian suppression/ablation with a gonadotropin-releasing hormone (GnRH) agonist; OR
    Note: Examples of a GnRH agonist include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant).
  - **b)** Patient has had surgical bilateral oophorectomy or ovarian irradiation; AND

CC) Patient meets ONE of the following criteria (i, ii, or iii):

- **i.** Verzenio will be used in combination with anastrozole, exemestane, or letrozole; OR
- **ii.** Verzenio will be used in combination with fulvestrant; OR
- **iii.** Patient meets the following conditions (a, b, and c):
  - **a)** Verzenio will be used as monotherapy; AND
  - **b)** Patient's breast cancer has progressed on at least one prior endocrine therapy; AND
    Note: Examples of prior endocrine therapy include anastrozole, exemestane, letrozole, tamoxifen, toremifene, exemestane plus everolimus, fulvestrant, everolimus plus fulvestrant or tamoxifen, megestrol acetate, fluoxymesterone, ethinyl estradiol.
  - **c)** Patient has tried chemotherapy for metastatic breast cancer.

***** Refer to the Policy Statement.

3. Breast Cancer - Recurrent or Metastatic in Men*. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):

A) Patient is ≥ 18 years of age; AND

B) Patient has recurrent or metastatic breast cancer; AND

C) Patient has hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}]disease; AND

D) Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND

E) Patient meets ONE of the following criteria (i, ii, or iii):

- **i.** Patient meets BOTH of the following conditions (a and b):

a) Patient is receiving a gonadotropin-releasing hormone (GnRH) analog; AND
Note: Examples of a GnRH analog include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Firmagon (degarelix acetate subcutaneous injection), Orgovyx (relugolix tablet).

b) Verzenio will be used in combination with anastrozole, exemestane, or letrozole; OR

- **ii.** Verzenio will be used in combination with fulvestrant; OR
- **iii.** Patient meets the following conditions (a, b, and c):
  - **a)** Verzenio will be used as monotherapy; AND
  - **b)** Patient's breast cancer has progressed on at least one prior endocrine therapy; AND
    Note: Examples are anastrozole, exemestane, letrozole, tamoxifen, toremifene, exemestane plus everolimus, fulvestrant, everolimus plus fulvestrant or tamoxifen, megestrol acetate, fluoxymesterone, ethinyl estradiol.
  - **c)** Patient has tried chemotherapy for metastatic breast cancer.

***** Refer to the Policy Statement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Verzenio is not recommended in the following situations:

35. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

30. Verzenio® tablets [prescribing information]. Indianapolis, IN: Eli Lilly; March 2023.
31. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – February 7, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 10, 2023.
32. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 10, 2023. Search terms: abemaciclib.

GnRH – Gonadotropin-releasing hormone.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Vistogard Prior Authorization Policy
- Vistogard® (uridine triacetate oral granules – Wellstat Therapeutics)

REVIEW DATE: 07/12/2023

OVERVIEW

Vistogard, a pyrimidine analog, is indicated for the emergency treatment of adult and pediatric patients for the following uses:[1]

- **Fluorouracil or capecitabine overdose**, regardless of the presence of symptoms.
- **Early-onset, severe or life-threatening toxicity** affecting the cardiac or central nervous system, and/or early-onset, unusually severe adverse reactions (e.g., gastrointestinal toxicity, neutropenia) within 96 hours following the end of fluorouracil or capecitabine administration.

As a limitation of use, Vistogard is not recommended for the non-emergent treatment of adverse events associated with fluorouracil or capecitabine because it may diminish the efficacy of these drugs.[1] The safety and efficacy of Vistogard initiated more than 96 hours following the end of fluorouracil or capecitabine administration have not been established.

Disease Overview

Fluorouracil and capecitabine (a fluorouracil prodrug) are widely used chemotherapeutic agents with potential for significant toxicity. Exaggerated sensitivity to capecitabine or fluorouracil may occur due to genetic variations in certain enzymes, renal impairment, or other causes.[2] Toxicity results in tissue damage, often manifesting as ulcerative mucositis with neutropenia leading to sepsis, shock, and organ failure. Additionally, central neurotoxicity and cardiac toxicity may occur without any identifiable predisposing factors. Exogenous uridine competes with the toxic metabolite fluorouridine triphosphate for incorporation into RNA in normal tissues, thereby protecting the tissues from toxicity.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vistogard. All approvals are provided for the duration noted below.

Automation: None

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vistogard is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Capecitabine or Fluorouracil Overdose.** Approve for 7 days.

2. **Capecitabine or Fluorouracil Toxicity, Severe or Life-Threatening.** Approve for 7 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vistogard is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

82. Vistogard® oral granules [prescribing information]. Rockville, MD: Wellstat Therapeutics; February 2017.
83. Ma WW, Saif MW, El-Rayes BF, et al. Emergency use of uridine triacetate for the prevention and treatment of life-threatening 5-fluorouracil and capecitabine toxicity. *Cancer.* 2017;123(2):345-356.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Vitrakvi Prior Authorization Policy
- Vitrakvi® (larotrectinib capsules and oral solution – Bayer)

REVIEW DATE: 01/25/2023

OVERVIEW

Vitrakvi, a kinase inhibitor, is indicated in adult and pediatric patients for treatment of **solid tumors** that: have a **neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion** without a known acquired resistance mutation; are metastatic or where surgical resection is likely to result in severe morbidity; and have no satisfactory alternative treatments or that have progressed following treatment.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) Compendium notes Vitrakvi as an option for the treatment of the following cancers with *NTRK* gene fusion-positive tumors as category 2A recommendations: ampullary adenocarcinoma, breast cancer, central nervous system cancers, cervical cancer, cholangiocarcinoma (intrahepatic and extrahepatic), colon cancer, cutaneous melanoma, endometrial carcinoma, epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer, Erdheim-Chester disease, esophageal and esophagogastric cancer, gallbladder cancer, gastric cancer, gastrointestinal stromal tumors, hepatocellular carcinoma, Langerhans Cell histiocytosis, neuroendocrine and adrenal tumors, non-small cell lung cancer, pancreatic cancer, rectal cancer, Rosai-Dorfman disease, salivary gland tumors, small bowel adenocarcinoma, soft tissue sarcoma, thyroid carcinoma, uterine sarcoma, and vulvar cancer.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vitrakvi. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vitrakvi is recommended in those who meet the following criteria:

FDA-Approved Indication

4. Solid Tumors. Approve for 1 year if the patient meets the following criteria (A and B):
Note: Examples of solid tumors include breast cancer, colon cancer, hepatobiliary cancer, histiocytic neoplasm, ovarian cancer, pancreatic cancer, salivary gland tumors, thyroid cancer, and rectal cancer.
- **A)** The tumor is positive for neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion; AND
- **B)** Patient meets one of the following criteria (i or ii):
  - **i.** The tumor is metastatic; OR
  - **ii.** Surgical resection of tumor will likely result in severe morbidity.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vitrakvi is not recommended in the following situations:

36. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

84. Vitrakvi® capsules and oral solution [prescribing information]. Whippany, NJ: Bayer; December 2022.
85. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed January 20, 2023. Search terms: larotrectinib.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Vizimpro Prior Authorization Policy
- Vizimpro® (dacomitinib tablets – Pfizer)

REVIEW DATE: 11/29/2023

OVERVIEW

Vizimpro, a tyrosine kinase inhibitor, is indicated for the first-line treatment of patients with metastatic **non-small cell lung cancer (NSCLC)** with epidermal growth factor receptor (*EGFR*) exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test.[1]

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines for NSCLC (version 5.2023 – November 8, 2023) recommend testing for sensitizing *EGFR* mutations in patients with metastatic disease.[2] Patients with sensitizing *EGFR* mutations have a significantly better response to the *EGFR* tyrosine kinase inhibitors (TKIs) [erlotinib, Gilotrif®, Iressa®, Tagrisso®, and Vizimpro]. The most common *EGFR* mutations are exon 19 deletions and exon 21 (L858R) substitution mutations. Other less common mutations that are also sensitive to *EGFR* TKIs include L861Q, G719X, and S768I; these mutations cumulatively account for approximately 10% of all *EGFR* mutations. NCCN recommends the *EGFR* TKIs as first-line treatment for patients with advanced or metastatic NSCLC with *EGFR* exon 19 deletions, exon 21 (L858R) substitution mutations, L861Q, G719X, and S768I.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vizimpro. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vizimpro is recommended in those who meet the following criteria:

FDA-Approved Indication

20. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets the following (A, B, and C):
- **DD)** Patient is ≥ 18 years of age; AND
- **EE)** Patient has advanced or metastatic disease; AND
- **FF)** Patient has sensitizing *EGFR* mutation-positive non-small cell lung cancer as detected by an approved test.

  Note: Examples of sensitizing *EGFR* mutation-positive non-small cell lung cancer include the following: exon 19 deletions, exon 21 (L858R) substitution mutations, L861Q, G719X, and S768I.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vizimpro is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Vizimpro® tablets [prescribing information]. New York, NY: Pfizer; December 2020.
2. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 5.2023 – November 8, 2023) © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 27, 2023.
3. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 27, 2023. Search term: dacomitinib.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Vonjo Prior Authorization Policy
- Vonjo™ (pacritinib capsules – CTI BioPharma)

REVIEW DATE: 03/22/2023

OVERVIEW

Vonjo, an inhibitor of Janus Associated Kinase (JAK)2 and FMS-like tyrosine kinase, is indicated for the treatment of intermediate- or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis with a platelet count below 50×10^9/L in adults.

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines for myeloproliferative neoplasms (version 3.2022 – August 11, 2022) classify risk stratification into two groupings: lower-risk disease and higher-risk disease.[2] NCCN guidelines recommend Vonjo for symptomatic lower-risk myelofibrosis if platelet count is $< 50 \times 10^9$/L with no response or loss of response to Jakafi® (ruxolitinib tablets), Pegasys® (peginterferon alfa-2a subcutaneous injection), or hydroxyurea. Vonjo is recommended for higher-risk myelofibrosis if the patient is not a transplant candidate and platelet count is $< 50 \times 10^9$/L; and if platelet count is $\geq 50 \times 10^9$/L in situations where the patient did not respond to or lost response to one prior JAK inhibitor (Jakafi or Inrebic® [fedratinib capsules]).[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vonjo. All approvals are provided for the duration noted below.

Automation: none

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vonjo is recommended in those who meet the following criteria:

FDA-Approved Indication

21. Myelofibrosis, including Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, and Post-Essential Thrombocythemia Myelofibrosis. Approve for 1 year if the patient meets the following criteria (A and B):

D) Patient is ≥ 18 years of age; AND

E) Patient meets one of the following criteria (i or ii):

a) Patient has a platelet count of less than 50×10^9/L (< 50,000/mcL) and meets one of the following criteria (a or b):

a) Patient meets both of the following criteria (1 and 2):

(1) Patient has intermediate-risk or high-risk disease; AND

(2) Patient is not a candidate for transplant; OR

b) Patient meets both of the following criteria (1 and 2):

(1) Patient has lower-risk disease; AND

(2) Patient has tried at least one prior therapy; OR

Note: Examples of prior therapy include: Jakafi (ruxolitinib tablets), Pegasys (peginterferon alfa-2a subcutaneous injection), and hydroxyurea.

b) Patient has a platelet count of greater than or equal to 50×10^9/L ($\geq$ 50,000/mcL) and meets all of the following criteria (a, b, and c):
- **a)** Patient has high-risk disease; AND
- **b)** Patient is not a candidate for transplant; AND
- **c)** Patient has tried Jakafi (ruxolitinib tablets) or Inrebic (fedratinib capsules).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vonjo is not recommended in the following situations:

37. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

86. Vonjo™ capsules [prescribing information]. Seattle, WA: CTI BioPharma; February 2022.
87. The NCCN Myeloproliferative Neoplasms Clinical Practice Guidelines in Oncology (version 3.2022 – August 11, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 13, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Votrient Prior Authorization Policy
- Votrient® (pazopanib tablets – GlaxoSmithKline)

REVIEW DATE: 06/14/2023

OVERVIEW

Votrient, a multi-tyrosine kinase inhibitor, is indicated in adults for the following uses:[1]
- **Renal cell carcinoma,** advanced.
- **Soft tissue sarcoma**, advanced, for patients who have received prior chemotherapy.

Guidelines

Votrient is discussed in guidelines from the National Comprehensive Cancer Network (NCCN)[2]:
- **Bone Cancer**: NCCN guidelines (version 3.2023 – April 4, 2023) recommend Votrient as a systemic therapy agent as "other recommended" regimens for chondrosarcoma for metastatic and widespread disease (category 2A).[3]
- **Gastrointestinal Stromal Tumor**: NCCN guidelines (version 1.2023 – March 13, 2023) recommend Votrient as an additional option after failure on approved therapies as "useful in certain circumstances" (category 2A).[4] The first line therapies are imatinib or Ayvakit™ (avapritinib tablets; for patients with *PDGFRA* exon 18 mutation, including the *PDGFRA* D842V mutation); second-line therapy is sunitinib or Sprycel® (dasatinib tablets; for *PDGFRA* exon 18 mutations that are insensitive to imatinib [including the *PDGFRA D842V* mutation]); third-line therapy is Stivarga® (regorafenib tablets); fourth-line therapy is Qinlock® (ripretinib tablets). The guidelines also state in a footnote that for unresectable disease, sunitinib, Stivarga, and Votrient are special considerations for succinate dehydrogenase (SDH)-deficient GIST (category 2A).[4]
- **Kidney Cancer**: NCCN guidelines (version 4.2023 – January 18, 2023) recommend Votrient as first-line and subsequent therapy for relapsed or stage IV disease for clear cell histology and as systemic therapy for non-clear cell histology as "useful in certain circumstances" (category 2A).[5] Votrient is also recommended as a single-agent therapy for von Hippel-Lindau-associated renal cell carcinoma as useful in certain circumstances (category 2A).
- **Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer**: NCCN guidelines (version 2.2023 – June 2, 2023) recommend Votrient (category 2B) as single-agent therapy for persistent disease or recurrence.[6]
- **Soft Tissue Sarcoma**: NCCN guidelines (version 2.2023 – April 25, 2023) recommend Votrient as single agent therapy for alveolar soft part sarcoma, angiosarcoma, desmoid tumors (aggressive fibromatosis), and solitary fibrous tumor/hemangiopericytoma.[7] Votrient is also recommended for dermatofibrosarcoma protuberans with fibrosarcomatous transformation for patients who are ineligible for intravenous systemic therapy or patients who are not candidates for anthracyclines-based regimens. For soft tissue sarcoma subtypes with non-specific histology, the guidelines recommend Votrient as first-line therapy for advanced and metastatic for patients who are ineligible for intravenous systemic therapy or patients who are not candidates for anthracyclines-based regimens and as a subsequent line of therapy for advanced or metastatic disease as palliative therapy as a single-agent (category 2A) or in combination with gemcitabine (category 2B).
- **Thyroid Carcinoma**: NCCN guidelines (version 2.2023 – May 18, 2023) for differentiated thyroid carcinoma recommend Votrient (category 2A) for progressive and/or symptomatic disease for unresectable locoregional recurrent or persistent disease not amenable to radioactive iodine therapy or distant metastatic disease not amendable to radioactive iodine therapy.[8] For differentiated

thyroid cancer subtypes, the guidelines have changed the naming of Hürthle cell neoplasm to oncocytic carcinoma. Votrient can be considered for treatment of progressive or symptomatic medullary thyroid disease if clinical trials or preferred systemic therapy options are not available or appropriate, or if there is progression on preferred systemic therapy options.

- **Uterine Neoplasms**: NCCN guidelines (version 2.2023 – April 28, 2023) recommend Votrient for as a systemic therapy option for uterine sarcoma as other recommended regimen for patients with recurrent or metastatic disease that have progressed on prior cytotoxic chemotherapy (category 2A).[9]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Votrient. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Votrient is recommended in those who meet one of the following criteria:

FDA-Approved Indications

22. Renal Cell Cancer. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets one of the following criteria (i or ii):
  - **i.** Patient has relapsed or advanced disease; OR
  - **ii.** Patient has von Hippel-Lindau disease.

2. Soft Tissue Sarcoma. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient does not have gastrointestinal stromal tumor; AND
  Note: If patient has gastrointestinal stromal tumor, see criteria 4 for gastrointestinal stromal tumor.
- **C)** Patient has advanced or metastatic disease; AND
- **D)** Patient has ONE of the following criteria (i, ii, iii, iv, v, vi, or vii):
  - **i.** Alveolar soft part sarcoma; OR
  - **ii.** Angiosarcoma; OR
  - **iii.** Desmoid tumors (aggressive fibromatosis); OR
  - **iv.** Dermatofibrosarcoma protuberans with fibrosarcomatous transformation; OR
  - **v.** Non-adipocytic sarcoma; OR
  - **vi.** Pleomorphic rhabdomyosarcoma; OR
  - **vii.** Solitary fibrous tumor/hemangiopericytoma.

Other Uses with Supportive Evidence

3. Bone Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has chondrosarcoma; AND
- **C)** Patient meets the following criteria (i and ii):
  - **i.** Patient has metastatic disease; AND
  - **ii.** According to the prescriber, patient has widespread disease.

4. **Gastrointestinal Stromal Tumor.** Approve for 1 year if the patient meets the following criteria (A and B):
   C) Patient is ≥ 18 years of age; AND
   D) Patient meets one of the following criteria (i or ii):
      i. Patient has succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumor; OR
      ii. Patient has tried each of the following (a, b, c, and d):
         a) One of imatinib or Ayvakit (avapritinib tablets); AND
         b) One of sunitinib or Sprycel (dasatinib tablets); AND
         c) Stivarga (regorafenib tablets); AND
         d) Qinlock (ripretinib tablets).

5. **Ovarian Cancer, Fallopian Tube, or Primary Peritoneal Cancer.** Approve for 1 year if the patient meets the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has persistent or recurrent disease.

6. **Thyroid Carcinoma, Differentiated.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has differentiated thyroid carcinoma; AND
   Note: Examples of differentiated thyroid carcinoma include papillary, follicular, and oncocytic carcinoma (formerly Hürthle cell carcinoma).
   C) Patient is refractory to radioactive iodine therapy.

7. **Thyroid Carcinoma, Medullary.** Approve for 1 year if the patient meets the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has tried at least one systemic therapy.
   Note: Examples of systemic therapy include Caprelsa (vandetanib tablets), Cometriq (cabozantinib capsules), Retevmo (selpercatinib capsules), and Gavreto (pralsetinib capsules).

8. **Uterine Sarcoma.** Approve for 1 year if the patient meets the following (A, B, and C):
   Note: Examples of uterine sarcoma include endometrial stromal sarcoma, undifferentiated uterine sarcoma, or uterine leiomyosarcomas.
   A) Patient is ≥ 18 years of age; AND
   B) Patient has recurrent or metastatic disease; AND
   C) Patient has tried at least one systemic regimen.
   Note: Examples of a systemic regimen include one or more of the following: doxorubicin, docetaxel, gemcitabine, ifosfamide, dacarbazine, epirubicin, or vinorelbine.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Votrient is not recommended in the following situations:

38. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Votrient® tablets [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; December 2021.

2. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 13, 2023. Search term: pazopanib.
3. The NCCN Bone Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – April 4, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. . Accessed June 13, 2023.
4. The NCCN Gastrointestinal Stromal Tumors Clinical Practice Guidelines in Oncology (version 1.2023 – March 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. . Accessed June 13, 2023.
5. The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – January 18, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. . Accessed June 13, 2023.
6. The NCCN Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – June 2, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. . Accessed June 13, 2023.
7. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. . Accessed June 13, 2023.
8. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (version 2.2023 – May 18, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. . Accessed June 13, 2023.
9. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (version 2.2023 – April 28, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 13, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Welireg Prior Authorization Policy
- Welireg™ (belzutifan tablets – Merck)

REVIEW DATE: 09/13/2023; selected revision 12/20/2023

OVERVIEW

Welireg, a hypoxia-inducible factor inhibitor, is indicated for the treatment of:

- **Renal cell carcinoma**, **advanced** following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI) in adults.
- **von Hippel-Lindau (VHL) disease,** in adults who require therapy for associated renal cell carcinoma, central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors, not requiring immediate surgery.[1]

The pivotal trial for VHL disease included patients with VHL disease-associated renal cell carcinoma, CNS hemangioblastomas, pancreatic neuroendocrine tumor, and retinal hemangioblastoma.[2]

Guidelines

Welireg is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):

- **CNS Cancers:** Guidelines (version 1.2023 – March 24, 2023) recommend Welireg for VHL-associated CNS hemangioblastoma not requiring immediate surgery as "useful in certain circumstances" (category 2A).[3]
- **Kidney Cancer:** Guidelines (version 1.2024 – June 21, 2023) recommend Welireg as a "preferred" regimen for VHL-associated renal cell carcinoma (category 2A) and single-agent therapy for relapse or stage IV disease as subsequent therapy for clear cell histology as "useful in certain circumstances" (category 2B)[4]
- **Neuroendocrine and Adrenal Tumors:** Guidelines (version 1.2023 – August 2, 2023) list VHL disease as a hereditary endocrine neoplasia. Welireg is recommended in a variety of settings for pancreatic neuroendocrine tumors with germline VHL alteration (category 2A).[5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Welireg. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Welireg is recommended in those who meet the following criteria:

FDA-Approved Indications

23. Renal Cell Carcinoma. Approved for 1 year if the patient meets the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has advanced disease; AND

C) Patient has tried at least one programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor; AND

Note: Examples of PD-1 inhibitor or PD-L1 inhibitor include: Keytruda (pembrolizumab intravenous infusion), Opdivo (nivolumab intravenous infusion), and Bavencio (avelumab intravenous infusion).

D) Patient has tried at least one vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).

Note: Examples of VEGF-TKI include Cabometyx (cabozantinib tablets), Lenvima (lenvatinib capsules), Inlyta (axitinib tablets), Fotivda (tivozanib capsules), pazopanib, sunitinib, and sorafenib

24. Von Hippel-Lindau Disease. Approve for 1 year if the patient meets the following (A, B, C and D):

A) Patient is ≥ 18 years of age; AND

B) Patient has a von Hippel-Lindau (VHL) germline alteration as detected by genetic testing; AND

C) Patient does not require immediate surgery; AND

D) Patient requires therapy for ONE of the following conditions (i, ii, iii, or iv):

i. Central nervous system hemangioblastomas; OR

ii. Pancreatic neuroendocrine tumors; OR

iii. Renal cell carcinoma; OR

iv. Retinal hemangioblastoma.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Welireg is not recommended in the following situations:

39. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

10. Welireg™ tablets [prescribing information]. Whitehouse Station, NJ: Merck; December 2023.
11. Jonasch E, Donskov F, Iliopoulos O, et al. Belzutifan for renal cell carcinoma in von Hippel-Lindau disease. *N Eng J Med.* 2021; 385(22): 2036-2046.
12. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 1.2023 – March 24, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 12, 2023.
13. The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (version 1.2024 – June 21, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 12, 2023.
14. The NCCN Neuroendocrine and Adrenal Tumors Clinical Practice Guidelines in Oncology (version 1.2023 – August 2, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on September 12, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Xalkori Prior Authorization Policy
- Xalkori® (crizotinib capsules and oral pellets – Pfizer)

REVIEW DATE: 01/11/2023; selected revision 11/22/2023

OVERVIEW

Xalkori, an oral kinase inhibitor, is indicated for the following uses:[1]

- **Anaplastic large cell lymphoma (ALCL)**, treatment of relapsed or refractory, systemic ALCL that is anaplastic lymphoma kinase (*ALK)*-positive in pediatric patients ≥ 1 year of age and young adults.
- **Inflammatory Myofibroblastic tumor (IMT),** treatment of unresectable, recurrent, or refractory inflammatory myofibrobastic tumor that is *ALK*-positive in patients ≥ 1 year of age.
- **Non-small cell lung cancer (NSCLC)**, metastatic, whose tumors are *ALK*-positive or *ROS* proto-oncogene 1 (*ROS1)*-positive as detected by an FDA-approved test in adults.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines address the use of Xalkori:[5-8]

- **Histiocytic Neoplasms:** Guidelines (version 1.2022 – May 20, 2022) recommend Xalkori as a "useful in certain circumstances" treatment option for the following types of histiocytic neoplasm with *ALK* rearrangement/fusion: Langerhans cell histiocytosis, Erdheim-Chester disease, and Rosai-Dorfman disease (category 2A).[3]
- **Inflammatory Myofibroblastic Tumor (IMT):** NCCN Soft Tissue Sarcoma guidelines (version 2.2022 – May 17, 2022) and NCCN Uterine Neoplasms guidelines (version 1.2023 – December 22, 2022) recommend Xalkori as a treatment option for IMT with *ALK* translocation.[4,5]
- **Melanoma: Cutaneous:** Guidelines (version 1.2023 – December 22, 2022) recommend Xalkori as a treatment option for cutaneous melanoma with *ALK* or *ROS1* fusions.[6]
- **NSCLC:** Guidelines (version 1.2023 – December 23, 2022) recommend Xalkori as a treatment option for *ALK* rearrangement-positive NSCLC and as a treatment option for NSCLC with mesenchymal-epithelial transition (*MET*) exon 14 skipping mutation or high-level *MET* amplification.[7]
- **T-Cell Lymphoma:** Guidelines (version 1.2023 – January 5, 2023) recommend Xalkori as a treatment option for relapsed or refractory *ALK*-positive ALCL.[7] NCCN notes that Xalkori also demonstrated activity in adults with relapsed or refractory *ALK*-positive ALCL, after at least one line of prior cytotoxic therapy.[8]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Xalkori. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Xalkori is recommended in those who meet one of the following criteria:

FDA-Approved Indications

2. **Anaplastic Large Cell Lymphoma.** Approve for 1 year if the patient meets the following (A, B, and C):
   A) Patient is ≥ 1 year of age; AND
   B) Patient has anaplastic lymphoma kinase (*ALK*)-positive disease; AND
   C) Patient meets one of the following (i or ii):
      i. Patient has relapsed disease; OR
      ii. Patient has refractory disease.

3. **Inflammatory Myofibroblastic Tumor.** Approve for 1 year if the patient meets the following (A, B, and C):
   A) Patient is ≥ 1 year of age; AND
   B) Patient has anaplastic lymphoma kinase (*ALK*)-positive disease; AND
   C) Patient meets one of the following (i or ii):
      i. Patient has advanced, recurrent, or metastatic disease; OR
      ii. The tumor is inoperable.

4. **Non-Small Cell Lung Cancer – Anaplastic Lymphoma Kinase (*ALK*)-Positive.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has advanced or metastatic disease; AND
   C) Patient has anaplastic lymphoma kinase (*ALK*)-positive disease; AND
   D) The mutation was detected by an approved test.

5. **Non-Small Cell Lung Cancer – *ROS1* Rearrangement-Positive.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has advanced or metastatic disease; AND
   C) Patient has *ROS1* rearrangement-positive disease; AND
   D) The mutation was detected by an approved test.

Other Uses with Supportive Evidence

5. **Histiocytic Neoplasm.** Approve for 1 year if patient meets one of the following (A, B, and C).
   A) Patient is ≥ 18 years of age; AND
   B) Patient has anaplastic lymphoma kinase (*ALK*) rearrangement/fusion-positive disease; AND
   C) Patient meets one of the following (i, ii, or iii):
      i. Patient has Langerhans cell histiocytosis; OR
      ii. Patient had Erdheim-Chester disease; OR
      iii. Patient has Rosai-Dorfman disease.

6. **Melanoma, Cutaneous.** Approve for 1 year if patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets one of the following (i or ii):
      i. Patient has anaplastic lymphoma kinase (*ALK*) fusion disease; OR
      ii. Patient has *ROS1* fusion disease.

7. **Non-Small Cell Lung Cancer with Mesenchymal Epithelial Transition (*MET*) Mutation.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets one of the following (i or ii):
      i. Patient has non-small cell lung cancer with high level *MET* amplification; OR
      ii. Patient has non-small cell lung cancer with *MET* exon 14 skipping mutation.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xalkori is not recommended in the following situations:

40. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

46. Xalkori® capsules and oral pellets [prescribing information]. New York, NY: Pfizer; September 2023.
47. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 5, 2023. Search term: crizotinib.
48. The NCCN Histiocytic Neoplasms Clinical Practice Guidelines in Oncology (version 1.2022 – May 20, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 5, 2023.
49. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 2.2022 – May 17, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 5, 2023.
50. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022) © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 6, 2023.
51. The NCCN Melanoma: Cutaneous Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022 – May 17, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 6, 2023.
52. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 5, 2023.
53. The NCCN T-Cell lymphomas Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 5, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Xermelo Prior Authorization Policy
- Xermelo™ (telotristat ethyl tablets – Lexicon)

REVIEW DATE: 06/14/2023

OVERVIEW

Xermelo, an inhibitor of tryptophan hydroxylase, is indicated for the treatment of **carcinoid syndrome diarrhea** in combination with somatostatin analog therapy in adults inadequately controlled by somatostatin analog therapy.[1]

The efficacy of Xermelo was evaluated in patients with metastatic neuroendocrine tumor and carcinoid syndrome diarrhea who were having between 4 to 12 daily bowel movements despite the use of somatostatin analog therapy at a stable dose for at least 3 months.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for treatment of neuroendocrine and adrenal tumors (version 2.2022 – December 21, 2022) state that Xermelo can be considered in combination with Sandostatin® LAR Depot (octreotide subcutaneous injection) or Somatuline® Depot (lanreotide subcutaneous injection) for persistent diarrhea due to poorly controlled carcinoid syndrome.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Xermelo. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xermelo is recommended in those who meet the following criteria:

FDA-Approved Indication

25. Carcinoid Syndrome Diarrhea. Approve for 1 year if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve if the patient meets all of the following criteria (i, ii, and iii):
- **i.** Patient has been on a long-acting somatostatin analog therapy for at least 3 consecutive months; AND
  Note: Examples of long-acting somatostatin analog therapy are Somatuline Depot (lanreotide subcutaneous injection) and Sandostatin LAR Depot (octreotide subcutaneous injection).
- **ii.** While on a long-acting somatostatin analog therapy (prior to starting Xermelo), the patient continues to have at least four bowel movements per day; AND
- **iii.** Xermelo will be used concomitantly with a long-acting somatostatin analog therapy.

B) Patient is Currently Receiving Xermelo. Approve if the patient is continuing to take Xermelo concomitantly with a long-acting somatostatin analog therapy for carcinoid syndrome diarrhea.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xermelo is not recommended in the following situations:

41. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

54. Xermelo™ tablets [prescribing information]. The Woodlands, TX: Merck; September 2022.
55. The NCCN Neuroendocrine and Adrenal Tumors Clinical Practice Guidelines in Oncology (version 2.2022 – December 21, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 7, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Xospata Prior Authorization Policy
- Xospata® (gilteritinib tablets – Astellas)

REVIEW DATE: 01/04/2023

OVERVIEW

Xospata, an inhibitor of tyrosine kinases including FMS-like tyrosine kinase 3 (*FLT3*), is indicated for the treatment of relapsed or refractory **acute myeloid leukemia** in adults with an *FLT3* mutation as detected by an FDA-approved test.[1]

Guidelines

Xospata is discussed in the National Comprehensive Cancer Network (NCCN) guidelines:

- **Acute Myeloid Leukemia:** NCCN guidelines (version 2.2022 – June 14, 2022) recommend Xospata in patients with relapsed or refractory disease and *FLT3*-internal tandem duplication (*FLT3-ITD*) or *FLT3*-tyrosine kinase domain (*FLT3-TKD*) mutation (category 1 for both).[2]
- **Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes:** NCCN guidelines (version 2.2022 – October 18, 2022) recommend Xospata for the treatment of myeloid/lymphoid neoplasms with eosinophilia and *FLT3* rearrangement in chronic phase or blast phase (category 2A). Xospata is also recommended in combination with acute lymphocytic leukemia- or acute myeloid leukemia-type induction chemotherapy followed by allogeneic hematopoietic cell transplantation (if eligible) for lymphoid, myeloid, or mixed lineage neoplasms with eosinophilia and *FLT3* rearrangement in blast phase (category 2A).[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Xospata. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xospata is recommended in those who meet one of the following criteria:

FDA-Approved Indications

13. Acute Myeloid Leukemia. Approve for 1 year if the patient meets the following criteria (A, B, and C).
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has relapsed or refractory disease; AND
- **C)** Disease is *FLT3*-mutation positive as detected by an approved test.

Other Uses with Supportive Evidence

14. Myeloid/Lymphoid Neoplasms. Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) Patient is ≥ 18 years of age; AND
B) Patient has eosinophilia; AND
C) Disease is *FLT3*-mutation positive as detected by an approved test.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xospata is not recommended in the following situations:

11. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available Condition.

REFERENCES

33. Xospata® tablets [prescribing information]. Northbrook, IL: Astellas Pharma; January 2022.
34. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 2.2022 – June 14, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 29, 2022.
35. The NCCN Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes Clinical Practice Guidelines in Oncology (version 2.2022 – October 18, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 29, 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Xpovio Prior Authorization Policy
- Xpovio® (selinexor tablets – Karyopharm Therapeutics)

REVIEW DATE: 03/01/2023

OVERVIEW

Xpovio, a nuclear export inhibitor, is indicated for treatment of the following conditions:[1]

- **Diffuse large B-cell lymphoma** (DLBCL), not otherwise specified (including DLBCL arising from follicular lymphoma), for treatment of relapsed or refractory disease in adults, after at least two lines of systemic therapy.
- **Multiple myeloma**:
  - In combination with dexamethasone for treatment of relapsed or refractory disease in adults who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.
  - In combination with bortezomib and dexamethasone, in adults who have received at least one prior therapy.

For DLBCL, Xpovio was approved under accelerated approval based on response rate. Continued approval may be contingent upon verification in a confirmatory trial(s).

Guidelines

Xpovio is addressed in the following guidelines from the National Comprehensive Cancer Network (NCCN):

- **B-Cell Lymphoma:** NCCN guidelines (version 2.2023 – February 8, 2023) recommend Xpovio as third-line and subsequent therapy of DLBCL (including for histologic transformation of indolent lymphomas to DLBCL), after at least two lines of systemic therapy.[3] This includes patients with disease progression after transplant or chimeric antigen receptor T-cell therapy.
- **Multiple Myeloma:** NCCN guidelines (version 3.2023 – December 8, 2022) recommend various regimens as primary therapy (transplant eligible and non-transplant candidates), maintenance therapy, and for previously treated multiple myeloma.[2] Xpovio/bortezomib/dexamethasone (once weekly) is among the "Other Recommended" regimens for previously treated disease following one to three previous therapies. Xpovio/dexamethasone after at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody, is recommended for patients with late relapses (> three prior therapies). Xpovio/Darzalex® (daratumumab injection)/dexamethasone, Xpovio/Kyprolis® (carfilzomib intravenous infusion)/dexamethasone, and Xpovio/Pomalyst® (pomalidomide capsules)/dexamethasone are among the regimens considered "Useful in Certain Circumstances" for previously treated multiple myeloma, for early relapses (one to three prior therapies).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Xpovio. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xpovio is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Diffuse Large B-Cell Lymphoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   Note: This includes patients with histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma.
   A) Patient is ≥ 18 years of age; AND
   B) Patient has been treated with at least two prior systemic therapies.

2. **Multiple Myeloma.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) The medication will be taken in combination with dexamethasone; AND
   C) Patient meets one of the following (i, ii, or iii):
   i. Patient has tried at least four prior regimens for multiple myeloma; OR
   ii. Patient meets both of the following (a and b):
   a) Patient has tried at least one prior regimen for multiple myeloma; AND
   b) The medication will be taken in combination with bortezomib; OR
   iii. Patient meets both of the following (a and b):
   a) Patient has tried at least one prior regimen for multiple myeloma; AND
   Note: Examples of prior regimens include bortezomib/Revlimid (lenalidomide capsules)/dexamethasone, Kyprolis (carfilzomib intravenous infusion)/Revlimid/dexamethasone, Darzalex (daratumumab intravenous infusion)/bortezomib or Kyprolis/dexamethasone, or other regimens containing a proteasome inhibitor, immunomodulatory drug, and/or anti-CD38 monoclonal antibody.
   b) The medication will be taken in combination with Darzalex (daratumumab intravenous infusion), Darzalex Faspro (daratumumab and hyaluronidase-fihj subcutaneous injection), Kyprolis (carfilzomib intravenous infusion), or Pomalyst (pomalidomide capsules).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xpovio is not recommended in the following situations:

12. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

36. Xpovio® tablets [prescribing information]. Newton, MA: Karyopharm Therapeutics; June 2022.
37. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 3.2023 – December 8, 2022). © 2022 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 26, 2023.
38. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 2.2023 – February 8, 2023). © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 26, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Xtandi Prior Authorization Policy
- Xtandi® (enzalutamide capsules and tablets – Astellas/Pfizer)

REVIEW DATE: 04/05/2023; selected revision 11/29/2023

OVERVIEW

Xtandi is an androgen receptor inhibitor indicated for the treatment of patients with **castration-resistant prostate cancer (CRPC), metastatic castration-sensitive prostate cancer (mCSPC)**, and **non-metastatic castration-sensitive prostate cancer (nmCSPC)** with biochemical recurrence at high risk for metastasis (high-risk biochemical recurrence [high-risk BCR]).[1] For CRPC and mCSPC, patients should receive Xtandi with a concurrent gonadotropin-releasing hormone (GnRH) analog or should have had a bilateral orchiectomy. Patients with nmCSPC with high-risk BCR may be treated with or without a GnRH analog.

Guidelines

According to the National Comprehensive Cancer Network (NCCN) guidelines on prostate cancer (version 1.2023 – September 16, 2022), all patients with metastatic CRPC should continue androgen deprivation therapy to maintain castrate levels of serum testosterone (< 50 ng/dL).

- For patients with non-metastatic CRPC, if the prostate specific antigen doubling time is ≤ 10 months, Xtandi, Erleada® (apalutamide tablets), and Nubeqa® (darolutamide tablets) are all preferred category 1 recommended options.
- For patients with mCRPC adenocarcinoma, therapies are based on prior docetaxel or prior novel hormone therapy use.
    - No prior docetaxel and no prior novel hormone therapy: the preferred regimens are Xtandi (category 1), abiraterone (category 1 only if no visceral metastases), and docetaxel (category 1).
    - Prior docetaxel, but no prior novel hormone therapy: the preferred regimens include Xtandi or abiraterone (both category 1), and Jevtana® (cabazitaxel intravenous infusion) [category 2A].
    - Prior novel hormone therapy but no prior docetaxel: Xtandi, abiraterone, and abiraterone + dexamethasone are "other recommended regimens" (both category 2A).
    - Prior docetaxel and prior novel hormone therapy: All systemic therapies are category 2B if visceral metastases are present. Preferred regimens are Jevtana (category 1) and docetaxel rechallenge. Xtandi, abiraterone, and other secondary hormone therapy are "other recommended regimens" (all category 2A).
- For mCSPC androgen deprivation therapy in combination with Xtandi, abiraterone + steroid, Erleada, and docetaxel are all category 1 recommended preferred options. Yonsa® (abiraterone acetate) with methylprednisolone is a category 2B recommendation.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Xtandi. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xtandi is recommended in those who meet one of the following criteria:

FDA-Approved Indications

26. Prostate Cancer – Castration-Resistant (Metastatic or Non-Metastatic). Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following (i, ii, or iii):
  - **i.** The medication is used concurrently with a gonadotropin-releasing hormone (GnRH) agonist; OR
    Note: Examples of GnRH agonists include: leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Vantas (histrelin acetate subcutaneous implant).
  - **ii.** The medication is concurrently used with Firmagon (degarelix subcutaneous injection); OR
  - **iii.** Patient has had a bilateral orchiectomy.

2. Prostate Cancer – Metastatic, Castration-Sensitive. Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following (i, ii, or iii):
  - **i.** The medication is used concurrently with a gonadotropin-releasing hormone (GnRH) agonist; OR
    Note: Examples of GnRH agonists include: leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Vantas (histrelin acetate subcutaneous implant).
  - **ii.** The medication is concurrently used with Firmagon (degarelix subcutaneous injection); OR
  - **iii.** Patient has had a bilateral orchiectomy.

3. Prostate Cancer – Non-Metastatic, Castration-Sensitive. Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has biochemical recurrence and is at high risk for metastasis.
  Note: High-risk biochemical recurrence is defined as prostate-specific antigen (PSA) doubling time ≤ 9 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xtandi is not recommended in the following situations:

42. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

15. Xtandi® capsules and tablets [prescribing information]. Northbrook, IL: Astellas/Pfizer; November 2023.
2. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – September 16, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed April 2, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Yonsa Prior Authorization Policy
- Yonsa® (abiraterone acetate tablets – Sun Pharmaceutical)

REVIEW DATE: 07/12/2023

OVERVIEW

Yonsa, an androgen biosynthesis inhibitor, is indicated in combination with methylprednisolone for the treatment of patients with **metastatic castration-resistant prostate cancer (CRPC)**.[1]

Guidelines

The National Comprehensive Cancer Network guidelines on prostate cancer (version 1.2023 – September 16, 2022) recommend Yonsa for the following uses:[2]

- At initial diagnosis, for patients classified in the regional risk group (metastases in regional nodes [N1] with no distant metastases [M0]) and with a > 5 year expected patient survival, external beam radiation therapy (EBRT) + androgen deprivation therapy (ADT) [category 1] + Zytiga® (abiraterone acetate tablets) and prednisone (category 2A) or Yonsa and methylprednisolone (category 2B) are recommended options. ADT (without EBRT) ± Zytiga and prednisone is a category 2A recommended option in this setting; ADT + Yonsa and methylprednisolone is a category 2B recommendation.
- If patients are positive for distant metastasis (M1) and have castration-naïve disease, ADT + Zytiga and prednisone and ADT + docetaxel are both category 1 recommended options. ADT + Yonsa and methylprednisolone is a category 2B recommendation in this setting.
- For patients with metastatic CRPC and who have not received prior docetaxel or prior novel hormone therapy, Zytiga + prednisone (category 1 without visceral metastases and category 2A with visceral metastases) and Yonsa + methylprednisolone (category 2A) is recommended.
- For patients with metastatic CRPC who have received prior novel hormone therapy but no prior docetaxel, Zytiga + prednisone or Yonsa + methylprednisolone is recommended (category 2A); Zytiga + dexamethasone or Yonsa + dexamethasone is recommended in this setting if patients have had disease progression on either formulation of abiraterone (category 2A). If docetaxel was used previously but no prior hormone therapy, Zytiga + prednisone (category 1) or Yonsa + methylprednisolone (category 2A) is recommended. If docetaxel and prior novel hormone therapy were used, Zytiga + prednisone or Yonsa + methylprednisolone are recommended (category 2A without visceral metastases; category 2B with visceral metastases).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Yonsa. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Yonsa is recommended in those who meet the following criteria:

FDA-Approved Indication

3. **Prostate Cancer – Metastatic, Castration-Resistant.** Approve for 1 year if the patient meets the following (A and B):
   - **A)** The medication is used in combination with methylprednisolone or dexamethasone; AND
   - **B)** Patient meets ONE of the following (i, ii, or iii):
     - **i.** The medication is concurrently used with a gonadotropin-releasing hormone agonist; OR
       Note: Examples of GnRH agonists include: leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), or Vantas (histrelin acetate subcutaneous implant).
     - **ii.** The medication is concurrently used with Firmagon (degarelix subcutaneous injection); OR
     - **iii.** Patient has had a bilateral orchiectomy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Yonsa is not recommended in the following situations:

13. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

56. Yonsa® tablets [prescribing information]. Cranbury, NJ: Sun Pharmaceutical; March 2022.
57. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – September 16. 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 7, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Zejula Prior Authorization Policy
- Zejula™ (niraparib capsules and tablets – GlaxoSmithKline)

REVIEW DATE: 01/11/2023; selected revision 05/10/2023

OVERVIEW

Zejula, a poly (ADP-ribose) polymerase (PARP) inhibitor, is indicated for **ovarian, fallopian tube, or primary peritoneal cancer** for the following uses:[1,2]

- Maintenance treatment of adults with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.
- Maintenance treatment of adults with deleterious or suspected deleterious germline BReast CAncer gene (*BRCA)*-mutated recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

Guidelines

Zejula is discussed in the National Comprehensive Cancer Network (NCCN) guidelines:

- **Ovarian cancer:** NCCN guidelines (version 1.2023 – December 22, 2022) recommend Zejula for treatment of recurrent disease and for maintenance treatment.[2] For treatment of recurrent disease, monotherapy with Lynparza® (olaparib capsules), Rubraca® (rucaparib tablets), and Zejula are listed under other recommended regimens for both platinum-sensitive and platinum-resistant disease (all category 3).[3] Zejula is recommended following three or more lines of prior chemotherapy in patients whose cancer is associated with homologous recombination deficiency (HRD) defined by either a deleterious or suspected deleterious *BRCA* mutation or genomic instability and progression > 6 months after response to the last platinum-based chemotherapy. Zejula + bevacizumab (category 2B) is also listed under other recommended targeted therapy regimen for platinum-sensitive disease.[2] Maintenance recommendations following primary treatment apply to Stage II, III, or IV ovarian cancer after primary treatment if the patient is in complete or partial response. If bevacizumab was not used during primary therapy, Zejula is recommended (category 1 for *BRCA* mutation; category 2A for *BRCA* wild-type of unknown). There is a footnote for Zejula that states in the absence of a *BRCA* mutation, HRD status may provide information on the magnitude of benefit of PARP inhibitor therapy. If bevacizumab was used during primary therapy, Zejula is only recommended for patients with a *BRCA* mutation (category 2A). In patients with platinum-sensitive disease who have completed at least two lines of platinum-based therapy and have achieved a complete or partial response, Zejula, Rubraca, or Lynparza can be considered for maintenance therapy if PARP therapy has not previously been used.[2] There is a footnote that states Zejula is limited to those with a deleterious or suspected deleterious germline *BRCA* mutation (category 1).
- **Uterine Neoplasms:** NCCN guidelines (version 1.2023 – December 22, 2022) recommend Zejula, Lynparza, and Rubraca as single-agent second-line or subsequent therapies for *BRCA2*-altered uterine leiomyosarcoma, useful in certain circumstances (category 2A).[4]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Zejula. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Zejula is recommended in those who meet one of the following criteria:

FDA-Approved Indication

27. Ovarian, Fallopian Tube, or Primary Peritoneal Cancer – Maintenance Therapy. Approve for 1 year if the patient meets the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient is in complete or partial response after a platinum-based chemotherapy regimen; AND
  Note: Examples of chemotherapy regimens are carboplatin with gemcitabine, carboplatin with paclitaxel, cisplatin with gemcitabine.
- **C)** Patient meets one of the following criteria (i or ii):
  - **i.** Patient meets both of the following criteria (a and b):
    - **a)** Patient has recurrent disease; AND
    - **b)** Patient has a *BRCA* mutation; OR
  - **ii.** Patient is in complete or partial response to first-line primary treatment.

Other Uses with Supportive Evidence

2. Ovarian, Fallopian Tube, or Primary Peritoneal Cancer – Treatment. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has tried at least three prior chemotherapy regimens; AND
  Note: Examples of chemotherapy regimens are carboplatin/gemcitabine, carboplatin/liposomal doxorubicin, carboplatin/paclitaxel, cisplatin/gemcitabine, capecitabine, irinotecan.
- **C)** Patient has homologous recombination deficiency (HRD)-positive disease as confirmed by an approved test.
  Note: HRD-positive disease includes patients with *BRCA* mutation-positive disease.

3. Uterine Leiomyosarcoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has a *BRCA2* mutation; AND
- **C)** Patient has tried one systemic regimen.
  Note: Examples of a systemic regimen include one or more of the following products: dacarbazine, docetaxel, doxorubicin, epirubicin, gemcitabine, ifosfamide, vinorelbine.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Zejula is not recommended in the following situations:

43. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

56. Zejula™ capsules [prescribing information]. Triangle Park, NC: GlaxoSmithKline; December 2022.
57. Zejula™ tablets [prescribing information]. Triangle Park, NC: GlaxoSmithKline; April 2023.
58. The NCCN Ovarian Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed December 29, 2022
59. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed January 9, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Zelboraf Prior Authorization Policy
- Zelboraf® (vemurafenib tablets – Genentech/Daiichi Sankyo)

REVIEW DATE: 07/19/2023

OVERVIEW

Zelboraf, a BRAF inhibitor, is indicated in adults for the following indications:[1]
- **Erdheim-Chester disease**, for treatment of patients with the *BRAF V600* mutation.
- **Melanoma**, for treatment of unresectable or metastatic disease with *BRAF V600E* mutation as detected by an FDA-approved test.

Of note, Cotellic® (cobimetinib tablets) is a MEK inhibitor that is indicated to be given in combination with Zelboraf in a similar patient population with melanoma. Zelboraf is not recommended for use in patients with wild-type BRAF melanoma.

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines support use in multiple cancers.
- **Central Nervous System Cancers**: Guidelines (version 1.2023 – March 24, 2023) recommend a BRAF/MEK inhibitor combination (i.e., Tafinlar® [dabrafenib capsules]/Mekinist® [trametinib tablets] or Zelboraf/Cotellic) for treatment of *BRAF V600E* activation mutation in the following situations: adjuvant treatment of pilocytic astrocytoma, pleomorphic xanthoastrocytoma, or ganglioglioma; recurrent or progressive low-grade glioma; oligodendroglioma or isocitrate dehydrogenase-2 (*IDH2*)-mutant astrocytoma; and recurrent glioblastoma.[7] BRAF/MEK combination therapy is also recommended for melanoma with brain metastases. Guidelines for pediatric central nervous system (CNS) cancers (version 2.2023 – October 31, 2022) include targeted therapy with Zelboraf as adjuvant therapy or for recurrent or progressive disease, if the cancer has a *BRAF V600E* mutation (both category 2A).[8] In the adjuvant setting, Zelboraf is recommended under "other recommended regimens" for age < 3 years with BRAF V600E mutated disease.
- **Hairy Cell Leukemia:** Guidelines (version 1.2023 – August 30, 2022) for hairy cell leukemia list Zelboraf ± rituximab among the treatment options for relapsed or refractory disease and for progressive disease after relapsed/refractory therapy.[3] For initial therapy, Zelboraf + Gazyva (obinutuzumab intravenous infusion) has been added as a category 2A recommendation under "useful in certain circumstances" with a qualifier that it can be considered for patients who are unable to tolerate purine analogs including frail patients and those with active infection.
- **Histiocytic Neoplasms**: Guidelines (version 1.2022 – May 20, 2022) recommend Zelboraf (preferred) or Tafinlar (other recommended regimen) for *BRAF V600E*-mutated Erdheim-Chester disease and for multisystem, pulmonary, or CNS Langerhans cell histocytosis.[6]
- **Melanoma, Cutaneous:** Guidelines (version 2.2023 – March 10, 2023) for cutaneous disease recommend BRAF/MEK inhibitor combinations among the preferred therapies for first-line and subsequent treatment of metastatic or unresectable melanoma with a *V600*-activating mutation.[2] This combination is also recommended for adjuvant treatment (category 2B). While combination BRAF/MEK inhibition is preferred, if a combination is contraindicated, monotherapy with a BRAF inhibitor is an option, especially in patients who are not appropriate candidates for checkpoint immunotherapy. Zelboraf + Cotellic + Tecentriq (atezolizumab intravenous infusion) is a recommended combination that is "useful in certain circumstances" (category 2A).

- **Non-Small Cell Lung Cancer:** Guidelines (version 3.2023 – April 13, 2023) list Zelboraf among the first-line options for tumors with a *BRAF* mutation, particularly if combination therapy with Tafinlar + Mekinist is not tolerated.[4]
- **Thyroid Carcinoma:** Guidelines (version 2.2023 – May 18, 2023) list Zelboraf as a treatment option (category 2B) if cancer is not amenable to radioiodine treatment, for differentiated thyroid cancer (follicular, oncocytic, and papillary cancer subtypes) with a *BRAF V600* mutation.[5]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Zelboraf. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Zelboraf is recommended in those who meet one of the following criteria:

FDA-Approved Indications

7. **Erdheim-Chester Disease.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has *BRAF V600* mutation-positive disease.

8. **Melanoma.** Approve for 1 year if the patient meets the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has unresectable, advanced, or metastatic melanoma; AND
   C) Patient has *BRAF V600* mutation-positive disease.

Other Uses with Supportive Evidence

9. **Central Nervous System Cancer.** Approve for 1 year if the patient meets the following (A, B, and C):
   A) The medication is being used for one of the following (i, ii, or iii):
      i. Adjuvant treatment of one of the following (a, b, or c):
         a) Pilocytic astrocytoma; OR
         b) Pleomorphic xanthoastrocytoma; OR
         c) Ganglioglioma; OR
      ii. Recurrent or progressive disease for one of the following (a, b, c, or d):
         a) Glioma; OR
         b) Isocitrate dehydrogenase-2 (*IDH2*)-mutant astrocytoma; OR
         c) Oligodendroglioma; OR
         d) Glioblastoma; OR
      iii. Brain metastases due to melanoma; AND
   B) Patient has *BRAF V600* mutation-positive disease; AND
   C) The medication is prescribed in combination with Cotellic (cobimetinib tablets).

10. **Hairy Cell Leukemia.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets one of the following (i or ii):

i. Patient has tried at least one other systemic therapy for hairy cell leukemia; OR
Note: Examples of other systemic therapies include cladribine, Nipent (pentostatin injection), rituximab, Intron A (interferon alpha-2b injection).

ii. Patient meets both of the following (a and b):

i. Patient is unable to tolerate purine analogs (i.e., active infection, frail patients); AND
Note: Examples of purine analogs are cladribine, Nipent (pentostatin injection).

ii. Zelboraf is used in combination with Gazyva (obinutuzumab intravenous infusion) as initial therapy.

11. Histiocytic Neoplasm. Approve for 1 year if the patient meets the following (A, B, and C):
Note: For Erdheim-Chester disease, refer to FDA-approved indication.

D) Patient is ≥ 18 years of age; AND

E) Patient has Langerhans cell histiocytosis and one of the following (i, ii, or iii):

i. Multisystem disease; OR

ii. Pulmonary disease; OR

iii. Central nervous system lesions; AND

F) Patient has *BRAF V600* mutation-positive disease.

12. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets the following (A and B):

A) Patient is ≥ 18 years of age; AND

B) Patient has *BRAF V600E* mutation-positive disease.

13. Thyroid Carcinoma, Differentiated. Approve for 1 year if the patient meets the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient has differentiated thyroid carcinoma; AND
Note: Examples of differentiated thyroid carcinoma include papillary, follicular, and oncocytic carcinoma (formerly Hürthle cell carcinoma).

C) Patient has disease that is refractory to radioactive iodine therapy; AND

D) Patient has *BRAF* mutation-positive disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zelboraf is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

16. Zelboraf® tablet [prescribing information]. South San Francisco, CA: Genentech; May 2020.
17. The NCCN Melanoma Clinical Practice Guidelines in Oncology (version 2.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on July 15, 2023.
18. The NCCN Hairy Cell Leukemia Clinical Practice Guidelines in Oncology (version 1.2023 – August 30, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on July 16, 2023.
19. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – April 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on July 16, 2023.
20. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (version 2.2023 – May 18, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on July 15, 2023.
21. The NCCN Histiocytic Neoplasms Clinical Practice Guidelines in Oncology (version 1.2022 – May 20, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on July 15, 2023.
22. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 1.2023 – March 24, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on July 16, 2023.
23. The NCCN Pediatric Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 2.2023 – October 31, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on July 16, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Zolinza Prior Authorization Policy
- Zolinza® (vorinostat capsules – Merck)

REVIEW DATE: 08/02/2023

OVERVIEW
Zolinza, a histone deacetylase inhibitor, is indicated for the treatment of cutaneous manifestations of **cutaneous T-cell lymphoma** in patients who have progressive, persistent or recurrent disease on or following two systemic therapies.[1]

Guidelines
The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for **primary cutaneous lymphomas** (version 1.2023 – January 5, 2023) recommend Zolinza as a systemic therapy for mycosis fungoides/Sezary syndrome.[2,3] Zolinza can be used for primary treatment or for relapsed, persistent, or refractory disease.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Zolinza. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Zolinza is recommended in those who meet the following criteria:

FDA-Approved Indication

15. Cutaneous T-Cell Lymphoma including Mycosis Fungoides/Sezary Syndrome. Approve for 1 year.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Zolinza is not recommended in the following situations:

14. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

39. Zolinza® capsules [prescribing information]. Whitehouse Station, NJ: Merck & Co.; July 2022.
40. The NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 31, 2023.
41. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on Jul 31, 2023. Search term: vorinostat.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Zydelig Prior Authorization Policy
- Zydelig® (idelalisib tablets – Gilead)

REVIEW DATE: 06/28/2023

OVERVIEW

Zydelig, a phosphatidylinositol 3-kinase (PI3K) inhibitor, is indicated for relapsed **chronic lymphocytic leukemia (CLL)** in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other comorbidities.[1]

Limitations of use: Zydelig is not indicated and is not recommended for first-line treatment of any patient, including patients with CLL, small lymphocytic lymphoma (SLL), follicular lymphoma (FL), and other indolent non-Hodgkin lymphomas. Zydelig is not indicated and is not recommended in combination with bendamustine and rituximab, or in combination with rituximab for the treatment of patients with FL, SLL, and other indolent non-Hodgkin lymphomas.[1]

Guidelines

Zydelig is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):

- **CLL/SLL:** NCCN guidelines (version 3.2023 – June 12, 2023) recommend Zydelig with or without rituximab as "other recommended regimens" for relapsed or refractory disease after prior Bruton tyrosine kinase inhibitor and venetoclax-based regimens for patients without del(17p)/TP53 mutations and as second-line or third-line therapy for patients with del(17p)TP53 mutation (category 2A).[3] Many other agents have a more prominent role in the first-line management of CLL. The guidelines note that CLL and SLL are different manifestations of the same condition and are treated similarly.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zydelig. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zydelig is recommended in those who meet one of the following:

FDA-Approved Indication

28. Chronic Lymphocytic Leukemia. Approve for 1 year if the patient meets the following (A and B):

C) Patient is ≥ 18 years of age; AND

D) Patient has tried at least one systemic regimen.

Note: Examples of systemic regimens contain one or more of the following products: Imbruvica (ibrutinib capsules, tablets, and oral solution), Brukinsa (zanubrutinib capsules), Calquence (acalabrutinib tablets), Venclexta (venetoclax tablets), chlorambucil, Gazyva (obinutuzumab intravenous infusion), rituximab, fludarabine, cyclophosphamide, bendamustine, high-dose methylprednisolone, Campath (alemtuzumab intravenous infusion), or Arzerra (ofatumumab intravenous infusion).

Other Uses with Supportive Evidence

29. Small Lymphocytic Lymphoma. Approve for 1 year if the patient meets the following (A and B):

A) Patient is ≥ 18 years of age; AND

B) Patient has tried at least one systemic regimen.

Note: Examples of systemic regimens contain one or more of the following products: Imbruvica (ibrutinib capsules, tablets, or oral solution), Brukinsa (zanubrutinib capsules), Calquence (acalabrutinib tablets), Venclexta (venetoclax tablets), chlorambucil, Gazyva (obinutuzumab intravenous infusion), rituximab, fludarabine, cyclophosphamide, bendamustine, high-dose methylprednisolone, Campath (alemtuzumab intravenous infusion), or Arzerra (ofatumumab intravenous infusion).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zydelig is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

24. Zydelig® tablets [prescribing information]. Foster City, CA: Gilead Sciences; February 2022.
25. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (version 3.2023 – June 12, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 21, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Zykadia Prior Authorization Policy
- Zykadia® (ceritinib capsules and tablets – Novartis)

REVIEW DATE: 07/12/2023

OVERVIEW

Zykadia, a kinase inhibitor, is indicated for the treatment of adults with metastatic **non-small cell lung cancer** (NSCLC) whose tumors are anaplastic lymphoma kinase (*ALK*)-positive as detected by an FDA-approved test.[1]

GUIDELINES

Zykadia is addressed in National Comprehensive Cancer Network (NCCN) guidelines:[2-5]

- **Histiocytic Neoplasms:** Guidelines (version 1.2022 – May 20, 2022) recommend Zykadia as a "useful in certain circumstances" treatment option for *ALK*-positive Erdheim-Chester Disease (category 2A).[3]
- **Inflammatory Myofibroblastic Tumor (IMT):** NCCN Soft Tissue Sarcoma guidelines (version 2.2023 – April 25, 2023) and NCCN Uterine Neoplasms guidelines (version 2.2023 – April 28, 2023) recommend Zykadia as a treatment option for IMT with *ALK* translocation.[5,6]
- **NSCLC:** Guidelines (version 3.2023 – April 13, 2023) recommend testing for biomarkers (e.g., *ALK* rearrangement, *ROS* proto-oncogene 1 (*ROS1)* gene rearrangement) in eligible patients with NSCLC.[4]
  - *ALK* rearrangement-positive NSCLC: If *ALK* rearrangement is discovered prior to first-line systemic therapy, Zykadia is an "other recommended therapy" (category 1). If *ALK* rearrangement is discovered during first-line systemic therapy, options are to complete the planned systemic therapy (including maintenance therapy) or to interrupt the systemic therapy and treat with Zykadia (category 2A) or another *ALK* inhibitor. NCCN recommendations for patients with disease progression often include continuing the first-line targeted therapy, depending on type of progression.
  - *ROS1* rearrangement-positive NSCLC: If *ROS1* rearrangement is discovered prior to first-line systemic therapy, Zykadia is an "other recommended" first-line treatment option (category 2A). If *ROS1* rearrangement is discovered during first-line systemic therapy, options are to complete the planned systemic therapy (including maintenance therapy) or interrupt and treat with Zykadia (category 2A). For patients who progress on treatment, if they are asymptomatic, they may continue to receive the treatment they were previously receiving (including Zykadia) or switch to Lorbrena® (lorlatinib tablets). There are different recommendations for patients who are symptomatic, depending on type of progression.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zykadia. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zykadia is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. **Non-Small Cell Lung Cancer (NSCLC) – Anaplastic Lymphoma Kinase (*ALK*)-Positive.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has advanced or metastatic disease; AND
   - **C)** Patient has anaplastic lymphoma kinase (*ALK*)-positive disease; AND
   - **D)** The mutation is detected by an approved test.

Other Uses with Supportive Evidence

2. **Erdheim-Chester Disease.** Approve for 1 year if the patient meets the following (A and B):
   - **E)** Patient is ≥ 18 years of age; AND
   - **F)** Patient has anaplastic lymphoma kinase (*ALK*) rearrangement/fusion-positive disease.

3. **Inflammatory Myofibroblastic Tumor.** Approve for 1 year if the patients meets the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has anaplastic lymphoma kinase (*ALK*)-positive disease; AND
   - **C)** Patient meets one of the following (i or ii):
   - **i.** Patient has advanced, recurrent, or metastatic disease; OR
   - **ii.** The tumor is inoperable.

4. **Non-Small Cell Lung Cancer with *ROS1* Rearrangement.** Approve for 1 year if the patient meets the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has advanced or metastatic disease; AND
   - **C)** Patient has *ROS1* rearrangement-positive disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zykadia is not recommended in the following situations:

44. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

26. Zykadia® capsules and tablets [prescribing information]. East Hanover, NJ: Novartis; October 2021.
27. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 6, 2023. Search terms: ceritinib.
28. The NCCN Histiocytic Neoplasms Clinical Practice Guidelines in Oncology (version 1.2022 – May 20, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 7, 2023.
29. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – April 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 7, 2023.
30. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). ©2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 7, 2023.
31. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (version 2.2023 – April 28, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 7, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmic – Glaucoma – Prostaglandins Prior Authorization Policy

- Bimatoprost 0.03% ophthalmic solution – generic only
- Lumigan® (bimatoprost 0.01% ophthalmic solution – Allergan)
- Rocklatan™ (netarsudil 0.02%/latanoprost 0.005% ophthalmic solution – Aerie)
- Travatan® Z (travoprost 0.004% ophthalmic solution [benzalkonium chloride-free] – Novartis, generic)
- Vyzulta™ (latanoprostene bunod 0.024% ophthalmic solution – Bausch + Lomb)
- Xalatan® (latanoprost 0.005% ophthalmic solution – Pfizer, generic)
- Xelpros™ (latanoprost 0.005% ophthalmic emulsion – Sun)
- Zioptan® (tafluprost 0.0015% ophthalmic solution – Akorn, generic)

REVIEW DATE: 04/26/2023

OVERVIEW

The various ophthalmic prostaglandin products are indicated for the reduction of elevated intraocular pressure (IOP) in patients with **open-angle glaucoma** or **ocular hypertension**.[1-8] All of these are single-entity products, except Rocklatan, which is a combination product containing a rho kinase inhibitor (netarsudil) and a prostaglandin analog (latanoprost). Bimatoprost 0.03% ophthalmic solution is also marketed as Latisse®, indicated to treat hypotrichosis of the eyelashes by increasing their growth including length, thickness, and darkness.[9] Of note, Latisse is not included in this policy.

Glaucoma, a disease that damages the eye's optic nerve, is the leading cause of blindness in people > 60 years old.[10] Reduction of IOP, regardless of the pretreatment IOP, reduces the risk of disease progression.[11] In addition, IOP reduction may prevent the onset to early glaucoma in patients with ocular hypertension.

Normal-tension glaucoma is a form of open-angle glaucoma characterized by glaucomatous optic neuropathy in patients with IOP measurements consistently < 21 mmHg.[12] According to the Glaucoma Research Foundation, normal-tension glaucoma is also referred to as low-tension glaucoma or normal-pressure glaucoma.[13] Additionally, the American Academy of Ophthalmology guidelines on primary open-angle glaucoma include normal-tension glaucoma in the recommendations for care, stating that lowering IOP reduces the risk of developing primary open-angle glaucoma and slows the progression of primary open-angle glaucoma, including normal-tension open-angle glaucoma.[11]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of ophthalmic prostaglandins for patients < 60 years of age. This age edit (for patients < 60 years of age) is used to monitor for appropriate use and to screen for cosmetic use. Prescription benefit coverage of these products for cosmetic conditions is not recommended. All approvals are provided for the duration noted below. For patients ≥ 60 years of age, coverage will be approved at the point of service. Prior Authorization and prescription benefit coverage is not recommended for Latisse.

Automation: If the patient is < 60 years of age and does not have a of one ophthalmic glaucoma agent (e.g., beta blockers, alpha adrenergic agonists, carbonic anhydrase inhibitors) within the 720-day look-back period, coverage will be determined by Prior Authorization criteria.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of ophthalmic prostaglandins is recommended in those who meet one of the following criteria:

FDA-Approved Indications

15. Ocular Hypertension. Approve for 1 year.

16. Open-Angle Glaucoma. Approve for 1 year.
Note: Open-angle glaucoma includes normal-tension glaucoma, which is also referred to as low-tension glaucoma or normal-pressure glaucoma.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of an ophthalmic prostaglandin is not recommended in the following situations:

45. Cosmetic Conditions (e.g., eyelash growth). Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical pharmacy benefit.

46. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Xalatan® ophthalmic solution [prescribing information]. New York, NY: Pfizer; September 2020.
2. Lumigan® ophthalmic solution [prescribing information]. Madison, NJ: Allergan; March 2022.
3. Travatan® Z ophthalmic solution [prescribing information]. East Hanover, NJ: Novartis; May 2020.
4. Zioptan® ophthalmic solution [prescribing information]. Lake Forest, IL: Akorn; November 2018.
5. Vyzulta™ ophthalmic solution [prescribing information]. Bridgewater, NJ: Bausch + Lomb; May 2019.
6. Bimatoprost 0.03% ophthalmic solution [prescribing information]. Somerset, NJ: Micro Labs; March 2022.
7. Rocklatan™ ophthalmic solution [prescribing information]. Irvine, CA: Aerie; June 2020.
8. Xelpros™ ophthalmic emulsion [prescribing information]. Cranbury, NJ: Sun; February 2021.
9. Latisse® ophthalmic solution [prescribing information]. Madison, NJ: Allergan; August 2021.
10. Boyd K. Glaucoma. Available at: https://www.aao.org/eye-health/diseases/what-is-glaucoma. Last reviewed on December 6, 2022. Accessed on April 6, 2023.
11. Gedde SJ, Vinod K, Wright MW, et al. Primary open-angle glaucoma Preferred Practice Pattern® guidelines. The American Academy of Ophthalmology. 2020. Available at: http://www.aao.org/guidelines-browse?filter=preferredpracticepatterns. Accessed on April 6, 2023.
12. Stein JD, Challa P. Diagnosis and Treatment of Normal-Tension Glaucoma. Available at: https://www.aao.org/eyenet/article/diagnosis-treatment-of-normal-tension-glaucoma. Accessed on April 17, 2023.
13. Glaucoma Research Foundation. Normal-Tension Glaucoma. Last reviewed on October 29, 2017. Available at: https://www.glaucoma.org/glaucoma/normal-tension-glaucoma.php. Accessed on April 17, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Dry Eye Disease – Cyclosporine Products Prior Authorization Policy
- Cequa™ (cyclosporine 0.09% ophthalmic solution – Sun Pharmaceuticals)
- Restasis® (cyclosporine 0.05% ophthalmic emulsion – Allergan, generic)
- Restasis Multidose™ (cyclosporine 0.05% ophthalmic emulsion – Allergan)
- Vevye™ (cyclosporine 0.1% ophthalmic solution – Novaliq)

REVIEW DATE: 07/12/2023; selected revision 10/11/2023

OVERVIEW

Ophthalmic cyclosporine products are indicated for the treatment of signs and symptoms of dry eye disease.[1-4] Specifically, ophthalmic cyclosporine emulsion products are indicated to increase tear production in patients whose tear production is presumed to be suppressed due to **ocular inflammation associated with keratoconjunctivitis sicca**.[1,2] Cequa is indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye).[3] Vevye is indicated for the treatment of the signs and symptoms of dry eye disease.[4]

Dry eye disease refers to a group of disorders of the tear film that are due to reduced tear production or tear instability and are associated with ocular discomfort and inflammatory disease of the ocular surface.[5] Dry eye disease is also known as dry eye syndrome and keratoconjunctivitis sicca.

The safety and efficacy of Restasis have not been established in pediatric patients < 16 years of age.[1,2] Although both Cequa and Vevye are approved for use in patients ≥ 18 years of age per product labeling, these products have the same chemical moiety as Restasis.[1-4]

Guidelines

The American Academy of Ophthalmology (AAO) published a Preferred Practice Pattern® guidelines (2018) for dry eye syndrome.[5] The AAO notes that dry eye disease may develop as a result of systemic inflammatory diseases (e.g., Sjögren syndrome, autoimmune thyroid disease, or rheumatoid arthritis) and ocular surface disease (e.g., herpes simplex virus keratitis). The AAO classifies dry eye as mild, moderate, or severe, based on signs and symptoms of the disease. Treatment recommendations of dry eye disease are listed in a four-step progression but specific therapies may be chosen from any category, regardless of the level of disease severity, depending on provider experience and patient preference. Topical non-glucocorticoid immunomodulatory drugs (such as cyclosporine) are staged as a Step 2 recommendation within the guidelines. The AAO recommends the use of topical cyclosporine as one of the treatment options for dry eye disease related to Sjögren syndrome.

The AAO Preferred Practice Pattern® guidelines for blepharitis (2018) note that blepharitis is a chronic ocular inflammation that may be associated with abnormalities with the Meibomian gland.[6] Treatment of blepharitis includes use of warm compresses, eyelid cleansing/eyelid massages, topical and/or systemic antibiotics, and ophthalmic anti-inflammatory agents (e.g., corticosteroids, cyclosporine).

The AAO Preferred Practice Pattern® guidelines for conjunctivitis (2018) note that dry eye and blepharitis are the most frequent causes of conjunctival inflammation.[7] Ophthalmic cyclosporine can be used to treat dry eye syndrome associated with GVHD and different types of conjunctivitis.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of ophthalmic cyclosporine products. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of ophthalmic cyclosporine products is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. **Dry Eye Disease.** Approve for 1 year if the patient is ≥ 16 years of age.
   Note: Examples of dry eye disease include dry eye syndrome and keratoconjunctivitis sicca.

Other Uses with Supportive Evidence

2. **Dry Eye Conditions due to Systemic Inflammatory Diseases.** Approve for 1 year if the patient is ≥ 16 years of age.
   Note: Examples of systemic inflammatory diseases that could result in dry eye conditions include Sjögren syndrome, autoimmune thyroid disease, rheumatoid arthritis.

3. **Dry Eye Conditions due to Ocular Surface Diseases.** Approve for 1 year if the patient is ≥ 16 years of age.
   Note: Examples of ocular surface diseases that could result in dry eye conditions include blepharitis, conjunctivitis, herpes simplex keratitis, ocular graft-versus-host disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of cyclosporine ophthalmic products is not recommended in the following situations:

15. **Concomitant Use with Another Ophthalmic Cyclosporine Product, Miebo (perfluorohexyloctane ophthalmic solution), Tyrvaya (varenicline nasal solution), or Xiidra (lifitegrast ophthalmic solution).** There are no data to support the concomitant use of two (or three) ophthalmic cyclosporine products or the concomitant use of an ophthalmic cyclosporine product with Miebo, Tyrvaya, or Xiidra.
    Note: Ophthalmic cyclosporine products are Cequa, Restasis, and Vevye.

16. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

32. Restasis® ophthalmic emulsion 0.05% [prescribing information]. Irvine, CA: Allergan; July 2017.
33. Restasis Multidose™ ophthalmic emulsion 0.05% [prescribing information]. Irvine, CA: Allergan; July 2017.
34. Cequa™ ophthalmic solution [prescribing information]. Cranbury, NJ: Sun Pharmaceutical; October 2021.
35. Vevye™ ophthalmic solution, 0.1%. Irvine, CA: Novaliq; May 2023.
36. Akpek E, Amescua G, Farid M, et al. American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. Dry Eye Syndrome Preferred Practice Pattern®. *Ophthalmology*. 2019 Jan;126(1):286-334.
37. Amescua G, Akpek EK, Farid M, et al. American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. Blepharitis Preferred Practice Pattern®. *Ophthalmology*. 2019 Jan;126(1):P56-P93.

38. Varu DM, Rhee MK, Akpek EK, et al. American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. Conjunctivitis Preferred Practice Pattern®. *Ophthalmology*. 2019 Jan;126(1):P94-P169.

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Dry Eye Disease – Eysuvis Prior Authorization Policy
- Eysuvis® (loteprednol etabonate 0.25% ophthalmic suspension – Kala)

REVIEW DATE: 12/06/2023

OVERVIEW
Eysuvis, an ophthalmic corticosteroid, is indicated for the **short-term (up to 2 weeks) treatment of the signs and symptoms of dry eye disease**.[1]

Guidelines
Eysuvis is not addressed in guidelines. The American Academy of Ophthalmology published a Preferred Practice Pattern® (2018) for the treatment of dry eye syndrome.[3] For mild dry eyes, education and environmental modifications, artificial tear solutions, and eyelid therapy (warm compresses and eyelid scrubs) are listed as some of the treatment options. The guidelines note commercially available loteprednol etabonate 0.5% was used in a prospective, randomized study for a 2-week period. The study found a favorable effect in patients' dry eye symptoms and conjunctival hyperemia findings.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Eysuvis. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Eysuvis is recommended in those who meet the following criteria:

FDA-Approved Indication

16. Dry Eye Disease (Short-Term Treatment). Approve for 1 month if the patient has tried artificial tears.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Eysuvis is not recommended in the following situations:

17. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

42. Eysuvis™ ophthalmic suspension [prescribing information]. Watertown, MA: Kala; July 2022.
43. Korenfeld M, Nichols KK, Goldberg D, et al. Safety of KPI-121 ophthalmic suspension 0.25% in patients with dry eye disease: A pooled analysis of 4 multicenter, randomized, vehicle-controlled studies. *Cornea*. 2021 May 1;40(5):564-570.
44. Akpek EK, Amescua G, Farid M, et al. Dry Eye Syndrome Preferred Practice Pattern®. *Ophthalmology*. 2019 Jan;126(1):P286-P334.

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Dry Eye Disease – Lacrisert Prior Authorization Policy
- Lacrisert® (hydroxypropyl cellulose ophthalmic insert – Bausch & Lomb)

REVIEW DATE: 12/06/2023

OVERVIEW

Lacrisert, an ophthalmic insert made of hydroxypropyl cellulose, is indicated for moderate to severe dry eye syndromes, including keratoconjunctivitis sicca.[1] Lacrisert is indicated especially in patients who remain symptomatic after an adequate trial of therapy with artificial tear solutions. Lacrisert is also indicated for patients with: exposure keratitis, decreased corneal sensitivity, and recurrent corneal erosions.

Guidelines

The American Academy of Ophthalmology (AAO) published Preferred Practice Pattern® (2018) for the treatment of dry eye syndrome.[2] The AAO classifies dry eye as mild, moderate, or severe, based on signs and symptoms of the disease. Treatment recommendations of dry eye disease are listed in a four-step progression, but specific therapies may be chosen from any category regardless of the level of disease severity, depending on provider experience and patient preference. Slow-release hydroxypropyl cellulose inserts are recommended within the guidelines for moderate dry eye as occasionally helpful for patients who are unable to apply artificial tears.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lacrisert. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lacrisert is recommended in those who meet the following criteria:

FDA-Approved Indication

17. Ocular Conditions Associated with Moderate to Severe Dry Eye. Approve for 1 year if the patient has tried artificial tears.
Note: Examples of ocular conditions include decreased corneal sensitivity, dry eye syndrome, exposure keratitis, keratoconjunctivitis sicca, recurrent corneal erosions.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lacrisert is not recommended in the following situations:

18. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

45. Lacrisert® ophthalmic insert [prescribing information]. Bridgewater, NJ: Bausch & Lomb; October 2019.
46. Akpek EK, Amescua G, Farid M, et al. Dry Eye Syndrome Preferred Practice Pattern®. *Ophthalmology*. 2019 Jan;126(1):P286-P334.

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Dry Eye Disease – Miebo Prior Authorization Policy
- Miebo™ (perfluorohexyloctane ophthalmic solution – Bausch & Lomb)

REVIEW DATE: 06/14/2023

OVERVIEW

Miebo, a semifluorinated alkane, is indicated for the treatment of the signs and symptoms of **dry eye disease** (DED).[1] The safety and effectiveness of Miebo in pediatric patients < 18 years of age have not been established.

There are no data to support concomitant use of Miebo with other ophthalmic medications for DED (e.g., cyclosporine [Cequa™, Restasis®, Vevye™), Tyrvaya® (varencilcine nasal solution), Xiidra® (lifitegrast ophthalmic solution).

Guidelines

The American Academy of Ophthalmology (AAO) published a Preferred Practice Pattern for the treatment of dry eye syndrome (used interchangeably with DED) in 2018.[2] The AAO classifies dry eye as mild, moderate, or severe, based on signs and symptoms of the disease. Treatment recommendations for DED are listed in a four-step progression but specific therapies may be chosen from any category, regardless of the level of disease severity, depending on provider experience and patient preference.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Miebo. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Miebo is recommended in those who meet the following criteria:

FDA-Approved Indication

30. Dry Eye Disease. Approve for 1 year if the patient is ≥ 18 years of age.
Note: Examples of dry eye disease include dry eye syndrome.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Miebo is not recommended in the following situations:

19. Concomitant use with an ophthalmic cyclosporine product (Cequa, Restasis, Vevye), Tyrvaya (varenicline nasal solution), or Xiidra (lifitegrast ophthalmic solution). There are no data to support the concomitant use of Miebo with Cequa/Restasis/Vevye, Tyrvaya, or Xiidra.

20. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

39. Miebo™ ophthalmic solution [prescribing information]. Bridgewater, NJ: Bausch & Lomb; May 2023.
40. Akpek E, Amescua G, Farid M, et al. American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. Dry Eye Syndrome Preferred Practice Pattern®. *Ophthalmology*. 2019 Jan;126(1):286-334.

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Dry Eye Disease – Tyrvaya Prior Authorization Policy
- Tyrvaya™ (varenicline nasal solution – Oyster Point)

REVIEW DATE: 09/20/2023

OVERVIEW

Tyrvaya, a cholinergic agonist, is indicated for the treatment of the signs and symptoms of **dry eye disease**.[1] The safety and efficacy of Tyrvaya in pediatric patients have not been established.

Guidelines

The American Academy of Ophthalmology (AAO) published a Preferred Practice Pattern (2018) for the treatment of dry eye syndrome.[2] Tyrvaya is not addressed in these guidelines. The AAO classifies dry eye as mild, moderate, or severe, based on signs and symptoms of the disease. Treatment recommendations for dry eye disease are listed in a four-step progression; however, specific therapies may be chosen from any category, regardless of the level of disease severity, depending on provider experience and patient preference. For mild dry eyes, education and environmental modifications, artificial tear solutions, and eyelid therapy (warm compresses and eyelid scrubs) are listed as some of the treatment options. Medications such as an ophthalmic cyclosporine product (Restasis®, Cequa™) or Xiidra® (lifitegrast ophthalmic solution) are recommended in moderate dry eye disease.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tyrvaya. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tyrvaya is recommended in those who meet the following criteria:

FDA-Approved Indication

31. Dry Eye Disease. Approve for 1 year if the patient meets the ALL of the following (A, B, and C):
Note: Examples of dry eye disease include dry eye syndrome.
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has tried artificial tears; AND
- **C)** The medication is prescribed by or in consultation with an ophthalmologist or optometrist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tyrvaya is not recommended in the following situations:

21. **Concomitant Use With An Ophthalmic Cyclosporine Product, Miebo (perfluorohexyloctane ophthalmic solution), or Xiidra® (lifitegrast ophthalmic solution).** There are no data to support the concomitant use of Tyrvaya with an ophthalmic cyclosporine product, Miebo, or Xiidra.
    Note: Ophthalmic cyclosporine products are Cequa, Restasis, and Vevye.

22. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

41. Tyrvaya™ nasal solution [prescribing information]. Princeton, NJ: Oyster Point; October 2021.
42. Akpek E, Amescua G, Farid M, et al. American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. Dry Eye Syndrome Preferred Practice Pattern®. *Ophthalmology*. 2019 Jan;126(1):286-334.

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Dry Eye Disease – Xiidra Prior Authorization Policy
- Xiidra® (lifitegrast ophthalmic solution – Novartis)

REVIEW DATE: 09/20/2023

OVERVIEW

Xiidra, a lymphocyte function-associated antigen-1 (LFA-1) antagonist, is indicated for the treatment of the signs and symptoms of **dry eye disease**.[1] The safety and efficacy of Xiidra in pediatric patients have not been established.

Guidelines

The American Academy of Ophthalmology (AAO) published Preferred Practice Pattern (2018) for the treatment of dry eye syndrome.[2] The AAO classifies dry eye as mild, moderate, or severe, based on signs and symptoms of the disease. Treatment recommendations of dry eye disease are listed in a four-step progression but specific therapies may be chosen from any category, regardless of the level of disease severity, depending on provider experience and patient preference. Topical LFA-1 antagonist drugs (such as Xiidra) are staged as a Step 2 recommendation within the guidelines.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Xiidra. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xiidra is recommended in those who meet the following criteria:

FDA-Approved Indication

32. Dry Eye Disease. Approve for 1 year if the patient is ≥ 18 years of age.
Note: Examples of dry eye disease include dry eye syndrome.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xiidra is not recommended in the following situations:

23. Concomitant Use with an Ophthalmic Cyclosporine Product, Miebo (perfluorohexyloctane ophthalmic solution), or Tyrvaya (varenicline nasal solution). There are no data to support the concomitant use of Xiidra with an ophthalmic cyclosporine product, Miebo, or Tyrvaya.
Note: Ophthalmic cyclosporine products are Cequa, Restasis, and Vevye.

24. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

43. Xiidra® ophthalmic solution [prescribing information]. East Hanover, NJ: Novartis; June 2020.
44. Akpek E, Amescua G, Farid M, et al. American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. Dry Eye Syndrome Preferred Practice Pattern®. *Ophthalmology*. 2019 Jan;126(1):286-334.

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Durysta Prior Authorization Policy
- Durysta® (bimatoprost implant, for intracameral administration – Allergan)

REVIEW DATE: 04/19/2023

OVERVIEW

Durysta, a prostaglandin analog, is indicated for the reduction of intraocular pressure (IOP) in patients with **open-angle glaucoma** or **ocular hypertension**.[1]

Disease Overview

Glaucoma, a disease that damages the eye's optic nerve, is the leading cause of blindness in people > 60 years of age.[2] Reduction of IOP, regardless of the pretreatment IOP, reduces the risk of disease progression.[3] In addition, IOP reduction may prevent the onset of early glaucoma in patients with ocular hypertension.

Ophthalmic prostaglandins, beta-blockers, alpha-agonist (brimonidine), carbonic anhydrase inhibitors, rho kinase inhibitor (netarsudil), and fixed combination products are used to treat glaucoma.[3,4] The choice of product is influenced by potential cost, adverse event profile, dosing schedule, and the degree of pressure lowering needed.[3]

Dosing Considerations

Durysta, a biodegradable implant, is given as a single intracameral administration.[1] Durysta should not be re-administered to an eye that was previously treated with Durysta.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Durysta. All approvals are provided for one implant per treated eye (i.e., one implant per treated eye; maximum of two implants per patient). Note that a 1-month (30 days) approval duration is applied to allow for the one-time treatment of one or both eye(s). Because of the specialized skills required for evaluation and diagnosis of patients treated with Durysta as well as the monitoring required for adverse events and long-term efficacy, approval requires Durysta to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Durysta is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Ocular Hypertension.** Approve for a one-time use in each treated eye (i.e., one implant per treated eye; a total of two implants per patient) if the patient meets ALL of the following criteria (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient is not receiving re-treatment of eye(s) previously treated with Durysta; AND
   - **C)** Patient meets BOTH of the following criteria (i and ii):
     - **i.** Patient has tried at least two ophthalmic prostaglandins (either as monotherapy or as concomitant therapy) for the treatment of open-angle glaucoma or ocular hypertension; AND
       Note: Examples of ophthalmic prostaglandins include bimatoprost 0.03% ophthalmic solution, latanoprost 0.005% ophthalmic solution, travoprost 0.004% ophthalmic solution; Lumigan (bimatoprost 0.01% ophthalmic solution), Vyzulta (latanoprostene bunod 0.024% ophthalmic solution), Xelpros (latanoprost 0.005% ophthalmic emulsion), and tafluprost 0.0015% ophthalmic solution), Iyuzeh (latanoprost 0.005% ophthalmic solution), and Omlonti (omidenepag isopropyl 0.002% ophthalmic solution).
     - **ii.** Patient has tried at least two ophthalmic products (either as monotherapy or as concomitant therapy) from two different pharmacological classes for the treatment of open-angle glaucoma or ocular hypertension; AND
       Note: Examples of pharmacological classes of ophthalmic products for the treatment of open-angle glaucoma or ocular hypertension include beta-blockers, alpha-agonist (brimonidine), carbonic anhydrase inhibitors, and rho kinase inhibitor (netarsudil).
   - **D)** For each of the ophthalmic medications that were tried, the patient meets ONE of the following criteria (i or ii):
     - **i.** Patient has had inadequate efficacy to the previously tried ophthalmic products, according to the prescriber; OR
     - **ii.** Patient has experienced adverse event(s) severe enough to warrant discontinuation of the previously tried ophthalmic products, according to the prescriber; AND
   - **E)** The medication is prescribed by or in consultation with an ophthalmologist.

2. **Open-Angle Glaucoma.** Approve for a one-time use in each treated eye (i.e., one implant per treated eye; a total of two implants per patient) if the patient meets ALL of the following criteria (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient is not receiving re-treatment of eye(s) previously treated with Durysta; AND
   - **C)** Patient meets BOTH of the following criteria (i and ii):
     - **i.** Patient has tried at least two ophthalmic prostaglandins (either as monotherapy or as concomitant therapy) for the treatment of open-angle glaucoma or ocular hypertension; AND
       Note: Examples of ophthalmic prostaglandins include bimatoprost 0.03% ophthalmic solution, latanoprost 0.005% ophthalmic solution, travoprost 0.004% ophthalmic solution; Lumigan (bimatoprost 0.01% ophthalmic solution), Vyzulta (latanoprostene bunod 0.024% ophthalmic solution), Xelpros (latanoprost 0.005% ophthalmic emulsion), tafluprost 0.0015% ophthalmic solution, Iyuzeh (latanoprost 0.005% ophthalmic solution), and Omlonti (omidenepag isopropyl 0.002% ophthalmic solution).
     - **ii.** Patient has tried at least two ophthalmic products (either as monotherapy or as concomitant therapy) from two different pharmacological classes for the treatment of open-angle glaucoma or ocular hypertension; AND
       Note: Examples of pharmacological classes of ophthalmic products for the treatment of open-angle glaucoma or ocular hypertension include beta-blockers, alpha-agonist (brimonidine), carbonic anhydrase inhibitors, and rho kinase inhibitor (netarsudil).

D) For each of the ophthalmic medications that were tried, the patient meets ONE of the following criteria (i or ii):
- **i.** Patient has had inadequate efficacy to the previously tried ophthalmic products, according to the prescriber; OR
- **ii.** Patient has experienced adverse event(s) severe enough to warrant discontinuation of the previously tried ophthalmic products, according to the prescriber; AND

E) The medication is prescribed by or in consultation with an ophthalmologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Durysta is not recommended in the following situations:

25. Re-Treatment of Previously-Treated Eye(s). Durysta is approved for a one-time use in each treated eye. Repeat administration in previously treated eye(s) is not approvable.

26. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

60. Durysta® [prescribing information]. Madison, NJ: Allergan; November 2020.
61. Boyd K. Glaucoma. Available at: https://www.aao.org/eye-health/diseases/what-is-glaucoma. Last reviewed, December 6, 2022. Accessed on April 6, 2023.
62. Gedde SJ, Vinod K, Wright MW, et al. Primary open-angle glaucoma Preferred Practice Pattern® guidelines. The American Academy of Ophthalmology. 2020. Available at: https://www.aao.org/education/preferred-practice-pattern/primary-open-angle-glaucoma-ppp. Accessed on April 6, 2023.
63. Facts and Comparisons® Online. Wolters Kluwer Health, Inc.; 2023. Available at: https://fco.factsandcomparisons.com/lco/action/home. Accessed on April 6, 2023. Search terms: ophthalmic beta blockers, alpha agonists, prostaglandins, netarsudil.

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Gene Therapy – Luxturna Prior Authorization Policy
- Luxturna® (voretigene neparvovec-rzyl subretinal injection – Spark Therapeutics)

REVIEW DATE: 02/22/2023

OVERVIEW

Luxturna, an adeno-associated virus vector-based gene therapy, is indicated for the treatment of patients with confirmed **biallelic human retinal pigment epithelial 65 kDa protein (RPE65) mutation-associated retinal dystrophy**.[1] Patients must have viable retinal cells as determined by the treating physician(s).

Luxturna is made up of a live, non-replicating adeno-associated virus serotype 2 which has been genetically modified to express the human RPE65 gene.[1] Luxturna is designed to deliver a normal copy of the gene encoding RPE65 to cells of the retina in patients with reduced or absent levels of biologically active RPE65. Treatment with Luxturna is not recommended for patients younger than 12 months of age, because the retinal cells are still undergoing cell proliferation, and Luxturna would potentially be diluted or lost during cell proliferation. The safety and effectiveness of Luxturna have not been established in geriatric patients. Clinical studies of Luxturna for this indication did not include patients ≥ 65 years of age.

Disease Overview

Inherited retinal dystrophies are a broad group of genetic retinal disorders that are associated with progressive visual dysfunction.[2] RPE65 mutation-associated retinal dystrophy is associated with numerous discrete gene mutations and affects 1,000 to 2,000 patients in the US. Mutations in the RPE65 gene lead to reduced or absent levels of RPE65 isomerohydrolase activity.[1] The absence of RPE65 leads to the accumulation of toxic precursors, damage to RPE-producing cells, and, over time, damage to photoreceptors, progressing to near total blindness in most patients.

Dosing Information

The recommended dose of Luxturna for each eye is 1.5×10^{11} vector genomes (vg) administered once per eye by subretinal injection.[1] After completing a vitrectomy (removal of the vitreous gel that fills the eye cavity) and under direct visualization, a small amount of Luxturna is injected slowly until an initial subretinal bleb is observed; the remaining volume is then injected slowly until the total 0.3 mL is delivered. Luxturna should be injected into each eye on separate days within a close interval, but no less than 6 days apart.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Luxturna. All approvals are provided for one injection per eye. Note: A 1-month (30 days) approval duration is applied to allow for the one-time treatment of both eyes. Because of the specialized skills required for evaluation and diagnosis of a patient treated with Luxturna as well as the specialized training required for administration of Luxturna, approval requires Luxturna to be administered by a retinal specialist. All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation. Some clients have elected Embarc Benefit Protection. For these clients, the Medical Director will coordinate with eviCore to ensure the Embarc Benefit Protection portion of the review has been completed. If the Embarc Benefit Protection portion of

the review has not been completed, the Medical Director will route to Embarc@eviCore.com prior to completing the review.

Documentation: Documentation is required for use of Luxturna as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Luxturna is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Biallelic Human Retinal Pigment Epithelial 65 kDa Protein (RPE65) Mutation-Associated Retinal Dystrophy.** Approve for a one-time treatment course (i.e., a total of two injections, one injection in each eye) if the patient meets the following criteria (A, B, C, D, and E):
   - **A)** Patient has a genetically confirmed diagnosis of biallelic RPE65 mutation-associated retinal dystrophy **[documentation required]**; AND
   - **B)** Patient is ≥ 12 months of age and < 65 years of age **[documentation required]**; AND
   - **C)** Luxturna is administered by a retinal specialist **[documentation required]**; AND
   - **D)** Patient must have viable retinal cells as determined by the treating physician **[documentation required]**; AND
   - **E)** Patient is not receiving retreatment of eye(s) previously treated with Luxturna **[documentation required]**.

   Dosing. Approve the following dosing regimen (A and B):
   - **A)** One 1.5 x 10^{11} vector genomes (vg) injection administered by subretinal injection into each eye; AND
   - **B)** The doses for the first eye and the second eye are separated by at least 6 days (i.e., injection of the second eye occurs 6 or more days after injection of the first eye).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Luxturna is not recommended in the following situations:

47. **Retreatment of previously treated eye(s)**. Luxturna is for one time use in each eye. Repeat dosing in previously treated eye(s) is not approvable.

48. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

33. Luxturna® subretinal injection [prescribing information]. Philadelphia, PA: Spark Therapeutics; May 2022.
34. FDA news release. FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss. Published on: December 19, 2017. Page last updated: March 16, 2018. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-novel-gene-therapy-treat-patients-rare-form-inherited-vision-loss. Accessed on February 17, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Izervay Prior Authorization Policy
- Izervay™ (avacincaptad pegol intravitreal injection – Iveric)

REVIEW DATE: 08/16/2023

OVERVIEW

Izervay, a complement C5 inhibitor, is indicated for the treatment of **geographic atrophy (GA) secondary to age-related macular degeneration (AMD)**.[1]

Disease Overview

AMD, a chronic, multifactorial, progressive central retinal disease, is the leading cause of irreversible blindness in the elderly population.[2-4] GA is a chronic progressive degeneration of the macula and is an advanced stage of AMD.[4,5] Approximately 20% of individuals with AMD will develop GA. GA is characterized by localized atrophy of the outer retinal tissue and irreversible loss of photoreceptors, retinal pigment epithelium, and choriocapillaris.[4-6] Initially, the GA lesions appear in the perifoveal macula but over time, the lesions often expand and coalesce to include the fovea. As the atrophic area expands, visual function and/or acuity decreases. In the clinical studies, patients had GA secondary to AMD with a best-corrected visual acuity (BCVA) between 20/25 and 20/320.[7,8]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Izervay. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Izervay as well as the monitoring required for adverse events and long-term efficacy, approval requires Izervay to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Izervay is recommended in those who meet the following criteria:

FDA-Approved Indication

18. Geographic Atrophy. Approve for 1 year if the patient meets the following (A, B, and C):
- **A)** Patient has geographic atrophy secondary to age-related macular degeneration; AND
- **B)** Patient has a best corrected visual acuity (BCVA) in the affected eye of between 20/25 and 20/320 letters; AND
- **C)** The medication is administered by or under the supervision of an ophthalmologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Izervay is not recommended in the following situations:

27. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

47. Izervay™ intravitreal injection [prescribing information]. Parsippany, NJ: Iveric; August 2023.
48. Kawa M, Machalinska A, Roginska D, Machalinski R. Complement system in pathogenesis of AMD: dual player in degeneration and protection of retinal tissue. *J Immunol Res*. 2014;483960.
49. Rein DB, Wittenborn JS, Burke-Conte Z, et al. Prevalence of age-related macular degeneration in the US in 2019. *JAMA Ophthalmol*. 2022;140:1202-1208.
50. Nabbioso M, Lambiase A, Cerini A, et al. Therapeutic approaches with intravitreal injections in geographic atrophy secondary to age-related macular degeneration: current drugs and potential molecules. *Int J Molec Sciences*. 2019;20(7):169.
51. Shae YS, Krogh Nielsen M, Do DV, et al. Geographic atrophy. Available at: https://eyewiki.aao.org/Geographic_Atrophy#:~:text=Geographic%20atrophy%20(GA)%20is%20a,retinal%20pigment%20epithelium%20and%20choriocapillaris. Accessed on August 7, 2023.
52. Fleckenstein M, Mitchel P, Freud KB, et al. The progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2018;125:369-390.
53. Jaffe GJ, Westby K, Csaky KG, et al. C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: a randomized pivotal Phase 2/3 trial. *Ophthalmology*. 2021;128:576-586.
54. Data on file. Izervay – GATHER2 study. Iveric; received on August 7, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Syfovre Prior Authorization Policy
- Syfovre™ (pegcetacoplan intravitreal injection – Apellis)

REVIEW DATE: 03/01/2023

OVERVIEW

Syfovre, a complement 3 inhibitor, is indicated for the treatment of **geographic atrophy (GA) secondary to age-related macular degeneration (AMD)**.[1]

Disease Overview

AMD, a chronic, multifactorial, progressive central retinal disease, is the leading cause of irreversible blindness in the elderly population.[2,3] There are two types of AMD: exudative or neovascular ("wet") and nonexudative or ("dry"). GA, a chronic progressive degeneration of the macula, is an advanced stage of dry AMD.[3,4] GA is characterized by localized atrophy of the outer retinal tissue and irreversible loss of photoreceptors, retinal pigment epithelium, and choriocapillaris.[3-5] Initially, the GA lesions appear in the perifoveal macula but over time, the lesions often expand and coalesce to include the fovea.[5,6] Area of the lesions is associated with a corresponding loss of visual function.[6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Syfovre. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Syfovre as well as the monitoring required for adverse events and long-term efficacy, approval requires Syfovre to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Syfovre is recommended in those who meet the following criteria:

FDA-Approved Indication

19. Geographic Atrophy. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **D)** Patient has geographic atrophy secondary to age-related macular degeneration; AND
- **E)** Patient has a best corrected visual acuity (BCVA) of 24 letters or better using Early Treatment Diabetic Retinopathy Study (ETDRS) charts; AND

Note: BCVA of 24 letters or better is approximately 20/320 Snellen equivalent.
- **F)** The medication is administered by or under the supervision of an ophthalmologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Syfovre is not recommended in the following situations:

28. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

55. Syfovre™ intravitreal injection [prescribing information]. Waltham, MA: Apellis; February 2023.
56. Rein DB, Wittenborn JS, Burke-Conte Z, et al. Prevalence of age-related macular degeneration in the US in 2019. *JAMA Ophthalmol*. 2022;140:1202-1208.
57. Nabbioso M, Lambiase A, Cerini A, et al. Therapeutic approaches with intravitreal injections in geographic atrophy secondary to age-related macular degeneration: current drugs and potential molecules. *Int J Molec Sciences*. 2019;20(7):1693.
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59. Fleckenstein M, Mitchel P, Freud KB, et al. The progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2018;125:369-390.
60. Pfau M, Schmitz-Valckenberg S, Ribeiro R, et al. Association of complement C3 inhibitor pegcetacoplan with reduced photoreceptor degeneration beyond areas of geographic atrophy. *Sci Rep*. 2022;12:17870. doi: 10.1038/s41598-022-22404-9.

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Tepezza Prior Authorization Policy
- Tepezza™ (teprotumumab intravenous infusion – Horizon)

REVIEW DATE: 01/18/2023

OVERVIEW

Tepezza, an insulin-like growth factor-1 receptor (IGF-1R) antagonist, is indicated for the treatment of **thyroid eye disease**, regardless of thyroid eye disease activity or duration.[1]

The Tepezza labeling (indication) was revised in April 2023 to include "regardless of thyroid eye disease activity or duration".[1] This change was supported by data from a Phase IV study.[2,3] However, full analysis of the data is not yet available. Based on limited available data, criteria changes are not needed at this time.

Disease Overview

Thyroid eye disease is a progressive, vision-threatening autoimmune inflammatory disease of the eye and orbital tissues with predominant features of fibrosis and adipogenesis.[4] It is also recognized in literature as Graves' ophthalmopathy, Graves' orbitopathy, thyroid-associated ophthalmopathy, and thyroid orbitopathy. Thyroid eye disease is most commonly related to Graves' disease, it can also develop in patients with other thyroid diseases (e.g., Hashimoto's thyroiditis) and has a higher prevalence in women than men (16 per 100,000 vs. 3 per 100,000, respectively).[5] In active disease, orbital fibroblasts appear responsible for soft tissue enlargement by expressing potential pathogenic autoantigens, such as thyrotropin receptor and IGF-1R.[4] Activation of orbital fibroblasts leads to increased hyaluronic acid production, proinflammatory cytokine synthesis, and enhanced differentiation into either myofibroblasts or adipocytes. These processes result in inflammation, enlargement of extraocular muscles and expansion of orbital tissue and fat, which in turn cause forward displacement of the eye, resulting in proptosis and inflammation.[6] The degree of severity can be staged as mild, moderate-to-severe, or sight-threatening, following quantitative assessment of lid aperture width, proptosis measurement, diplopia score, degrees of abduction in eye muscle movement, examination of the cornea for evidence of exposure keratitis or ulceration, and assessment of optic nerve function.

Dosing Information

The recommended dose is 10 mg/kg administered by intravenous (IV) infusion for the initial dose, followed by 20 mg/kg administered intravenously once every 3 weeks for seven additional doses.[1]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tepezza. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tepezza as well as the monitoring required for adverse events and long-term efficacy, approval requires Tepezza to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tepezza is recommended in those who meet the following criteria:

FDA-Approved Indication

20. Thyroid Eye Disease. Approve for 6 months if the patient meets the following criteria (A, B, C, and D):
Note: Thyroid Eye Disease is also recognized as Graves' ophthalmopathy, Graves' orbitopathy, thyroid-associated ophthalmopathy, and thyroid orbitopathy.
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has been assessed as having active disease of at least moderate severity based on signs and symptoms, according to the prescriber; AND
  Note: Examples of active disease of at least moderate severity include the degree of inflammation, degree of proptosis, presentation of diplopia.
- **C)** Patient has not received 8 doses (total) of Tepezza; AND
  Note: The maximum recommended treatment is for 8 doses. For a patient who has started therapy but has not completed 8 doses, approve the number of doses required for the patient to receive a total of 8 doses.
- **D)** The medication is prescribed by or in consultation with an ophthalmologist, endocrinologist, or a physician who specializes in thyroid eye disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tepezza is not recommended in the following situations:

29. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

61. Tepezza intravenous infusion [prescribing information]. Lake Forest, IL: Horizon; April 2023.
62. Horizon Therapeutics. A study evaluating Tepezza treatment in patients with chronic (inactive) thyroid eye disease. In: ClinicalTrials.gov [internet]. Bethesda (MD): National Library of Medicine (US). 2023-04-20. Available at: https://clinicaltrials.gov/ct2/show/NCT04583735?cond=tepezza&draw=2&rank=1. NCT04583735. Accessed on May 18, 2023.
63. Press Release. Horizon Therapeutics plc announces positive topline data from Tepezza (teprotumumab-trbw) phase 4 clinical trial in patients with chronic/low clinical activity score (CAS) thyroid eye disease (TED). Released April 10, 2023. Available at: https://ir.horizontherapeutics.com/news-releases/news-release-details/horizon-therapeutics-plc-announces-positive-topline-data. Accessed on May 18, 2023.
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66. Shan S, Douglas R. The pathophysiology of thyroid eye disease. *J Neuroophthalmol*. 2014 Jun;34(2):177-85.

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Upneeq Prior Authorization Policy
- Upneeq® (oxymetazoline hydrochloride 0.1% ophthalmic solution –RVL Pharmaceuticals)

REVIEW DATE: 09/20/2023

OVERVIEW
Upneeq, an alpha-adrenergic agonist, is indicated for the treatment of **acquired blepharoptosis** in adults.[1]

Disease Overview and Clinical Efficacy
Blepharoptosis, also known as ptosis, is a common condition defined by abnormal drooping of one or both upper eyelids.[2,3] Overall incidence ranges from 4.7% to 13.5% in adults. Prevalence increases with age; a United Kingdom study reported that prevalence increased from 2.4% in patients 50 to 59 years of age to 20.8% in patients ≥ 70 years of age.[3] Blepharoptosis is either congenital or acquired (underlying etiology include involutional, neurogenic, myogenic, traumatic, or mechanical).[2,3] Transient ptosis can also occur following ocular procedures (e.g., cataract surgery). The most common cause of acquired ptosis is stretching, dehiscence, or disinsertion of the levator muscle complex related to aging. Ptosis can partially or completely affect vision and it can also affect patients' appearance, which can increase levels of anxiety and depression. Surgical interventions are the standard of care and are effective in improving the visual field. However, surgery may be associated with complications and risks of asymmetry, under- or over-correction which can require surgical revision, bleeding, and infection.

Guidelines
Upneeq is not addressed in guidelines. The American Academy of Ophthalmology issued a report (2011) detailing functional indications for upper eyelid ptosis and blepharoplasty surgery; various quantitative and qualitative criteria may be used to identify appropriate surgical candidates.[4] Surgical techniques vary and outcomes data are limited to low-level evidence (case series). Some studies have demonstrated median improvements of 13 points in the Leicester Peripheral Field Test (LPFT) score following surgical interventions.

POLICY STATEMENT
Due to insufficient clinical efficacy data, **approval of Upneeq is not recommended**. Current Upneeq efficacy information is insufficient to determine if the medication demonstrates any clinically meaningful benefits.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Upneeq is not recommended in the following situations:

30. **Blepharoptosis.** Due to insufficient clinical efficacy data, approval of Upneeq for treatment of blepharoptosis is not recommended. Upneeq was studied in two randomized, double-masked, placebo-controlled, multicenter Phase III studies (published) [n = 304].[1,2] Patients with acquired ptosis and superior visual field deficit in at least one eye at screening were randomized 2:1 to Upneeq or vehicle. Study medication was self-administered as a single drop per eye, once daily in the morning for 42 days (6 weeks). The primary endpoint was change from baseline in number of points seen in the top four rows on the Leicester Peripheral Field test (LPFT), which assesses superior visual field deficits due to ptosis on Day 1 (6 hours after instillation) and Day 14 (2 hours after instillation). The secondary endpoint was change from baseline in marginal reflex distance 1 (MRD1), which is the distance between the center of the papillary light reflex and the upper eyelid margin with the eye in primary gaze, on Days 1 and 14. Although Upneeq provided a statistically significant incremental benefit over vehicle in LPFT, the difference between the groups was small compared with what is typically observed following surgical interventions. Significantly greater, but numerically small, changes in MRD1 from baseline were observed in the Upneeq group vs. vehicle. It is unclear if these incremental changes (between Upneeq and vehicle) would correspond with clinically meaningful improvement. In addition, the studies were 6 weeks in duration (primary and secondary endpoints were assessed on Days 1 and 14); there are no long-term efficacy data for Upneeq for this condition. Upneeq's role in the management of patients with blepharoptosis is not established.

31. **Conjunctivitis.** Oxymetazoline solution 0.1% has not been evaluated for conjunctivitis.

32. **Cosmetic uses.** Coverage of Upneeq for cosmetic uses (i.e., blepharoptosis when functional limitation is absent) is not recommended as cosmetic uses are excluded from coverage in a typical pharmacy benefit.

33. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

67. Upneeq® ophthalmic solution [prescribing information]. Bridgewater, NJ: RVL Pharmaceuticals; May 2023.
68. Slonim CB, Foster S, Jaros M, Kannarr SR, et al. Association of oxymetazoline hydrochloride, 0.1%, solution administration with visual field in acquired ptosis: a pooled analysis of 2 randomized clinical trials. *JAMA Ophthalmol*. 2020 Nov 1;138(11):1168-1175.
69. Bacharach J, Wirta DL, Smyth-Medina R, et al. Rapid and sustained eyelid elevation in acquired blepharoptosis with oxymetazoline 0.1%: randomized phase 3 trial results. *Clin Ophthalmol*. 2021 Jun 25;15:2743-2751.
70. Cahill KV, Bradley EA, Meyer DR, et al. Functional indications for upper eyelid ptosis and blepharoplasty surgery: a report by the American Academy of Ophthalmology. *Ophthalmology*. 2011;118(12):2510-2517.

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Beovu Prior Authorization Policy
- Beovu® (brolucizumab-dbll intravitreal injection – Novartis)

REVIEW DATE: 11/15/2023

OVERVIEW

Beovu, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the following uses:[1]
- **Diabetic macular edema**.
- **Neovascular (wet) age-related macular degeneration**.

Other Uses with Supportive Evidence

Overproduction of VEGF may lead to other eye conditions, including neovascular glaucoma, retinopathy of prematurity, and other retinal and choroidal neovascular conditions affecting the eye.[2,3] The VEGF inhibitors have the potential to be used off-label to reduce or slow visual impairment or vision loss associated with other eye conditions related to increased VEGF production.[2,4,5] The use of anti-VEGF agents have been shown to stop the angiogenic process and maintain visual acuity and improve vision in patients with certain neovascular ophthalmic conditions; therefore, research is rapidly evolving on the use of VEGF inhibitors in other neovascular ophthalmic conditions which threaten vision.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Beovu. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Beovu as well as the monitoring required for adverse events and long-term efficacy, approval requires Beovu to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Beovu is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Diabetic Macular Edema.** Approve for 1 year if administered by or under the supervision of an ophthalmologist.

2. **Neovascular (Wet) Age-Related Macular Degeneration.** Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Other Uses with Supportive Evidence

3. Other Neovascular Diseases of the Eye. Approve for 1 year if administered by or under the supervision of an ophthalmologist.
Note: Examples of other neovascular diseases of the eye include neovascular glaucoma, retinopathy of prematurity, sickle cell neovascularization, choroidal neovascular conditions.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Beovu is not recommended in the following situations:

34. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

71. Beovu® intravitreal injection [prescribing information]. Hanover, NJ: Novartis; September 2023.
72. Barakat MR, Kaiser PK. VEGF inhibitors for the treatment of neovascular age-related macular degeneration. *Expert Opin Investig Drugs*. 2009;18(5):637-646.
73. Tolentino M. Systemic and ocular safety of intravitreal anti-VEGF therapies for ocular neovascular disease. *Surv Ophthalmol*. 2011;56(2):95-113.
74. Kinnunen K, Ylä-Herttuala S. Vascular endothelial growth factors in retinal and choroidal neovascular diseases. *Ann Med*. 2012;44(1):1-17.
75. Horsley MB, Kahook MY. Anti-VEGF therapy for glaucoma. *Curr Opin Ophthalmol*. 2010;21(2):112-117.

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Eylea and Eylea HD Prior Authorization Policy
- Eylea® (aflibercept intravitreal injection – Regeneron)
- Eylea® HD (aflibercept intravitreal injection – Regeneron)

REVIEW DATE: 11/15/2023

OVERVIEW

Eylea, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the following uses:[1]
- **Diabetic macular edema**.
- **Diabetic retinopathy**.
- **Macular edema following retinal vein occlusion**.
- **Neovascular (wet) age-related macular degeneration**.
- **Retinopathy of Prematurity**.

Eylea HD, a high dose VEGF inhibitor, is indicated for the following uses:[6]
- **Diabetic macular edema**.
- **Diabetic retinopathy**.
- **Neovascular (wet) age-related macular degeneration**.

Other Uses with Supportive Evidence for Eylea

Overproduction of VEGF may lead to other eye conditions, including neovascular glaucoma, retinopathy of prematurity, and other retinal and choroidal neovascular conditions affecting the eye.[2,3] The VEGF inhibitors have the potential to be used off-label to reduce or slow visual impairment or vision loss associated with other eye conditions related to increased VEGF production.[2,4,5] The use of anti-VEGF agents have been shown to stop the angiogenic process and maintain visual acuity and improve vision in patients with certain neovascular ophthalmic conditions; therefore, research is rapidly evolving on the use of VEGF inhibitors in other neovascular ophthalmic conditions which threaten vision.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Eylea and Eylea HD. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Eylea and Eylea HD as well as the monitoring required for adverse events and long-term efficacy, approval requires Eylea and Eylea HD to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Eylea is recommended in those who meet one of the following criteria:

FDA-Approved Indications

4. Diabetic Macular Edema. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

5. Diabetic Retinopathy. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

6. Macular Edema Following Retinal Vein Occlusion. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

7. Neovascular (Wet) Age-Related Macular Degeneration. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

8. Retinopathy of Prematurity. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Other Uses with Supportive Evidence

9. Other Neovascular Diseases of the Eye. Approve for 1 year if administered by or under the supervision of an ophthalmologist.
Note: Examples of other neovascular diseases of the eye include neovascular glaucoma, sickle cell neovascularization, and choroidal neovascular conditions.

II. Coverage of Eylea HD is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Diabetic Macular Edema.** Approve for 1 year if administered by or under the supervision of an ophthalmologist.

35. Diabetic Retinopathy. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

36. Neovascular (Wet) Age-Related Macular Degeneration. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Eylea and Eylea HD is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

76. Eylea® intravitreal injection [prescribing information]. Tarrytown, NY: Regeneron; August 2023.
77. Barakat MR, Kaiser PK. VEGF inhibitors for the treatment of neovascular age-related macular degeneration. *Expert Opin Investig Drugs*. 2009;18(5):637-646.
78. Tolentino M. Systemic and ocular safety of intravitreal anti-VEGF therapies for ocular neovascular disease. *Surv Ophthalmol*. 2011;56(2):95-113.
79. Kinnunen K, Ylä-Herttuala S. Vascular endothelial growth factors in retinal and choroidal neovascular diseases. *Ann Med*. 2012;44(1):1-17.
80. Horsley MB, Kahook MY. Anti-VEGF therapy for glaucoma. *Curr Opin Ophthalmol*. 2010;21(2):112-117.
81. Eylea® HD intravitreal injection [prescribing information]. Tarrytown, NY: Regeneron; August 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Ranibizumab Products Prior Authorization Policy
- Byooviz™ (ranibizumab-nuna intravitreal injection – Biogen)
- Cimerli™ (ranibizumab-eqrn intravitreal injection – Coherus)
- Lucentis® (ranibizumab intravitreal injection – Genentech)

REVIEW DATE: 11/15/2023

OVERVIEW

Lucentis and Cimerli (interchangeable biosimilar to Lucentis) are vascular endothelial growth factor (VEGF) inhibitors indicated for the following uses:[1,7]
- **Diabetic macular edema**.
- **Diabetic retinopathy**.
- **Macular edema following retinal vein occlusion**.
- **Myopic choroidal neovascularization**.
- **Neovascular (wet) age-related macular degeneration**.

Byooviz (interchangeable biosimilar to Lucentis) is indicated for the following uses:[6]
- **Macular edema following retinal vein occlusion**.
- **Myopic choroidal neovascularization**.
- **Neovascular (wet) age-related macular degeneration**.

Other Uses with Supportive Evidence

Overproduction of VEGF may lead to other eye conditions, including neovascular glaucoma, retinopathy of prematurity, and other retinal and choroidal neovascular conditions affecting the eye.[2,3] The VEGF inhibitors have the potential to be used off-label to reduce or slow visual impairment or vision loss associated with other eye conditions related to increased VEGF production.[2,4,5] The use of anti-VEGF agents have been shown to stop the angiogenic process and maintain visual acuity and improve vision in patients with certain neovascular ophthalmic conditions; therefore, research is rapidly evolving on the use of VEGF inhibitors in other neovascular ophthalmic conditions which threaten vision.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of ranibizumab products. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with ranibizumab products as well as the monitoring required for adverse events and long-term efficacy, approval requires ranibizumab products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of ranibizumab products is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Diabetic Macular Edema.** Approve for 1 year if administered by or under the supervision of an ophthalmologist.

2. **Diabetic Retinopathy.** Approve for 1 year if administered by or under the supervision of an ophthalmologist.

3. **Macular Edema Following Retinal Vein Occlusion.** Approve for 1 year if administered by or under the supervision of an ophthalmologist.

4. **Myopic Choroidal Neovascularization.** Approve for 1 year if administered by or under the supervision of an ophthalmologist.

5. **Neovascular (Wet) Age-Related Macular Degeneration.** Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Other Uses with Supportive Evidence

6. **Other Neovascular Diseases of the Eye.** Approve for 1 year if administered by or under the supervision of an ophthalmologist.
   Note: Examples of other neovascular diseases of the eye include neovascular glaucoma, retinopathy of prematurity, sickle cell neovascularization, choroidal neovascular conditions.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of ranibizumab products is not recommended in the following situations:

37. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

82. Lucentis® intravitreal injection [prescribing information]. South San Francisco, CA: Genentech; August 2023.
83. Barakat MR, Kaiser PK. VEGF inhibitors for the treatment of neovascular age-related macular degeneration. *Expert Opin Investig Drugs*. 2009;18(5):637-646.
84. Tolentino M. Systemic and ocular safety of intravitreal anti-VEGF therapies for ocular neovascular disease. *Surv Ophthalmol*. 2011;56(2):95-113.
85. Kinnunen K, Ylä-Herttuala S. Vascular endothelial growth factors in retinal and choroidal neovascular diseases. *Ann Med*. 2012;44(1):1-17.
86. Horsley MB, Kahook MY. Anti-VEGF therapy for glaucoma. *Curr Opin Ophthalmol*. 2010;21(2):112-117.
87. Byooviz™ intravitreal injection [prescribing information]. Cambridge, MA: Biogen; October 2023.
88. Cimerli™ intravitreal injection [prescribing information]. Redwood City, CA: Coherus; August 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Susvimo Prior Authorization Policy
- Susvimo™ (ranibizumab intravitreal injection via ocular implant – Genentech)

REVIEW DATE: 11/15/2023

OVERVIEW

Susvimo, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the treatment of patients with **neovascular** (wet) **age-related macular degeneration** (nAMD) who have previously responded to at least two intravitreal injections of a VEGF inhibitor.[1] In contrast to the other VEGF inhibitor products which are administered as intravitreal injections, Susvimo is an intravitreal implant.

Safety

Susvimo has a Boxed Warning regarding endophthalmitis, which occurred at a 3-fold higher rate with Susvimo vs. Lucentis (1.7% vs. 0.5% in active-controlled trials).[1] Additional Warnings associated with the implant and/or implant-related procedures unique to Susvimo include rhegmatogenous retinal detachment, implant dislocation, vitreous hemorrhage, conjunctival erosion or retraction, conjunctival bleb, postoperative decrease in visual acuity, air bubbles causing improper filling of the implant, and deflection of the implant. These Warnings/Precautions are unique to Susvimo (among the injectable VEGF inhibitor class) and in general, many of these Warnings/Precautions are associated with the Susvimo implant and/or other implant-related procedures.

POLICY STATEMENT

Due to the safety concerns, **approval is not recommended** for Susvimo. There are significant risks associated with use based on the Boxed Warning regarding endophthalmitis.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Susvimo is not recommended in the following situations:

38. Neovascular (Wet) Age-Related Macular Degeneration. Due to the safety data, approval is not recommended for Susvimo. In the pivotal trial, Susvimo demonstrated non-inferiority compared with Lucentis.[1-3] However, ocular adverse events were more frequent with Susvimo vs. Lucentis; patients treated with Susvimo require regular monitoring to evaluate for presence of these adverse events. Notably, Susvimo labeling includes a unique Boxed Warning regarding endophthalmitis, which was three times more frequent with Susvimo vs. Lucentis.

39. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

89. Susvimo™ intravitreal injection via ocular implant [prescribing information]. South San Francisco, CA: Genentech; April 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Verkazia Prior Authorization Policy
- Verkazia® (cyclosporine 0.1% ophthalmic emulsion – Santen)

REVIEW DATE: 01/18/2023

OVERVIEW

Verkazia, a calcineurin inhibitor immunosuppressant, is indicated for the treatment of **vernal keratoconjunctivitis** in patients ≥ 4 years of age.[1]

Guidelines

Verkazia is not addressed in guidelines. However, ophthalmic cyclosporine products (in strengths of 0.05% and 2%) are discussed for the treatment of vernal keratoconjunctivitis in the American Academy of Ophthalmology Conjunctivitis Preferred Practice Pattern recommendations (2018).[2] Commercially available 0.05% ophthalmic cyclosporine has demonstrated efficacy with more frequent dosing for the treatment of vernal conjunctivitis. It has been shown to reduce signs and symptoms, prevent seasonal recurrences, and may reduce use of topical steroids. Besides cyclosporine, other medications recommended for maintenance of vernal keratoconjunctivitis include ocular lubricants, antihistamines (oral and ophthalmic), and ophthalmic mast-cell stabilizers. Ophthalmic corticosteroids are reserved for acute exacerbations.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Verkazia. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Verkazia as well as the monitoring required for adverse events and long-term efficacy, approval requires Verkazia to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Verkazia is recommended in those who meet the following criteria:

FDA-Approved Indication

10. Vernal Keratoconjunctivitis. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 4 years of age; AND
- **B)** According to the prescriber, the patient has moderate to severe vernal keratoconjunctivitis; AND
- **C)** Patient meets one of the following (i or ii):
  - **i.** Patient has tried two single-action ophthalmic medications (i.e., ophthalmic mast-cell stabilizers or ophthalmic antihistamines) for the maintenance treatment of vernal keratoconjunctivitis; OR

Note: Examples of single-action ophthalmic medications for the maintenance treatment of vernal keratoconjunctivitis include ophthalmic mast-cell stabilizers (e.g., cromolyn ophthalmic solution, Alomide ophthalmic solution]) and ophthalmic antihistamines (e.g., Zerviate [cetirizine ophthalmic solution]).

ii. Patient has tried one dual-action ophthalmic mast-cell stabilizer/antihistamine product for the maintenance treatment of vernal keratoconjunctivitis; AND

Note: Examples of dual-action ophthalmic mast-cell stabilizer/antihistamine products include azelastine ophthalmic solution, beoptastine ophthalmic solution, epinastine ophthalmic solution, ketotifen ophthalmic solution, Lastacaft, and olopatadine ophthalmic solution.

Note: An exception to the requirement for a trial of two single-action ophthalmic medications (i.e., ophthalmic mast-cell stabilizers or ophthalmic antihistamines) or one dual-action ophthalmic mast-cell stabilizer/antihistamine product for the maintenance treatment of vernal keratoconjunctivitis can be made if the patient has already tried at least one ophthalmic cyclosporine product (e.g., Cequa [cyclosporine 0.09% ophthalmic solution], Restasis [cyclosporine 0.05% ophthalmic emulsion]) other than the requested medication.

D) The medication is prescribed by or in consultation with an optometrist or ophthalmologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Verkazia is not recommended in the following situations:

40. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

90. Verkazia® ophthalmic emulsion [prescribing information]. Emeryville, CA: Santen; June 2022.
91. Varu D, Rhee M, Akpek E, et al. American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. Conjunctivitis Preferred Practice Pattern®. *Ophthalmology*. 2019;126:P94-P169.

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Oxervate Prior Authorization Policy
- Oxervate™ (cenegermin-bkbj ophthalmic solution – Dompé)

REVIEW DATE: 06/14/2023

OVERVIEW

Oxervate, a recombinant human nerve growth factor, is indicated for the treatment of **neurotrophic keratitis**.[1]

Duration of Treatment

The recommended dosing regimen is one drop six times a day (at 2 hour intervals) for 8 weeks.[1] In one of the pivotal studies, five patients who experienced a recurrence of neurotrophic keratitis after an 8-week course of Oxervate were re-treated with another 8 weeks of Oxervate.[2] Four of these patients achieved corneal healing, which was maintained through the end of the follow-up period.

Disease Overview

Neurotrophic keratitis, a rare degenerative disease, is characterized by corneal epithelium breakdown, impairment of corneal healing, and development of corneal ulceration, melting, and perforation.[3-6] Corneal epithelial cells release various neurotrophic growth factors, including nerve growth factors, which are important in maintaining the integrity and function of the ocular surface and in stimulating both epithelial and nerve fiber proliferation and survival.[7,8] When corneal sensory innervation is impaired, reduction of both protective reflexes and trophic neuromodulators essential for the vitality, metabolism, and wound healing of the ocular surface tissues results. *In vivo* studies have shown that increasing nerve growth factor concentration after injury can accelerate healing.[4,8]

Guidelines/Recommendations

Neurotrophic keratosis is classified into three stages: Stage 1 (mild), corneal epithelial changes; Stage 2 (moderate), corneal epithelial defect; Stage 3 (severe), corneal ulcer, perforation, melting.[6] Prior to the approval of Oxervate, there were no approved pharmacologic therapies for the treatment of neurotrophic keratitis.[3] If neurotrophic keratitis is left untreated, the condition can progress to anatomical loss of the eye; even with treatment, loss of vision is common.[6,7] Treatment should target corneal sensory innervation impairment to restore corneal integrity; treatment goals are to stop progression and promote epithelial healing.

There are no formal clinical guidelines, although there are expert opinion on the diagnosis and treatment of neurotrophic keratitis.[6] Optimal care requires identifying and treating the underlying causes of neurotrophic keratitis; for example, using antiviral medications for herpetic disease, correcting eyelid abnormalities, controlling hemoglobin A1c levels in patients with diabetes, and providing supportive therapy for limbal stem cell deficiency. For all stages, optimal care includes discontinuation of all preservative-containing ophthalmic medications to the extent possible and use of preservative-free tear substitutes or lubricants is recommended. For patients with Stage 2 disease, Oxervate, prophylactic ophthalmic preservative-free antibiotics, oral tetracyclines (e.g., doxycycline), corneal therapeutic contact lenses, and fresh-frozen self-retained amniotic membrane may be considered. For patients with Stage 3 disease, all of the listed options for Stage 2 disease as well as synthetic tissue adhesive, tarsorrhaphy, amniotic membrane transplant, and corneal neurotization are optimal treatments.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Oxervate. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Oxervate as well as the monitoring required for adverse events and long-term efficacy, approval requires Oxervate to be prescribed by a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Oxervate is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Neurotrophic Keratitis.** Approve if the patient meets the following criteria (A or B):
   Note: The initial course is 8 weeks of treatment with Oxervate in the affected eye. If the patient has not yet received a total of 8 weeks of treatment in the affected eye, review under Initial Course. If the patient has already received at least 8 weeks of treatment in the affected eye, review under Recurrence.
   A) Initial Course. Approve up to 8 weeks per affected eye(s) if the patient meets the following criteria (i and ii):
   Note: For example, if the patient has already received 2 weeks of treatment with Oxervate, an additional 6 weeks may be approved. This allows for a total of 8 weeks of treatment per affected eye(s).
      i. Patient has previously received < 8 weeks of treatment in the affected eye(s); AND
      ii. The medication is prescribed by an ophthalmologist or optometrist; OR
   B) Recurrence. Approve up to 8 weeks per affected eye(s) if the patient meets the following criteria (i and ii):
   Note: For example, if the patient has already received 8 weeks of treatment with Oxervate, an additional 8 weeks may be approved. This allows for a total of 16 weeks of treatment per affected eye(s).
      i. Patient has previously received at least 8 weeks but less than 16 weeks of treatment per affected eye(s); AND
      ii. The medication is prescribed by an ophthalmologist or optometrist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Oxervate is not recommended in the following situations:

1. **Treatment Duration of > 16 Weeks Per Affected Eye(s).** Available data supports use of Oxervate for up to 16 weeks.[2,7]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Oxervate™ ophthalmic solution [prescribing information]. Boston, MA: Dompé; October 2019.
2. Pflugfelder SC, Massaro-Giordano M, Perez VL, et al. Topical recombinant human nerve growth factor (cenegermin) for neurotrophic keratopathy. A multicenter randomized vehicle-controlled pivotal trial. *Ophthalmology*. 2020;127:127:14-26
3. Oxervate. FDA Clinical Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761094Orig1s000TOC.cfm. Accessed on June 9, 2023.
4. Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of the corneal nerve. *J Cell Physiol*. 2017;232:717-724.
5. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthamol*. 2018;8:571-579.
6. Dana R, Farid M, Gupta PK, et al. Expert consensus on the identification, diagnosis, and treatment of neurotrophic keratopathy. *BMC Ophthalmology*. 2021;21:327-335
7. Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Progress in Retinal and Eye Research*. 2018;16:107-131.
8. Vesura P, Giannaccare G, Pellegrini M, et al. Neurotrophic keratitis: current challenges and future prospects. *Eye and Brain*. 2018;10:37-45.

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Vabysmo Prior Authorization Policy
- Vabysmo® (faricimab-svoa intravitreal injection – Genentech)

REVIEW DATE: 11/15/2023

OVERVIEW

Vabysmo, a vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2) inhibitor, is indicated for the following uses:[1]

- **Diabetic macular edema** (DME).
- **Macular edema following retinal vein occlusion (RVO).**
- **Neovascular (wet) age-related macular degeneration** (nAMD).

For the indication of macular edema following RVO, Vabysmo is recommended for use for 6 months.[1] The prescribing information does not note a duration of treatment for DME or nAMD.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vabysmo. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vabysmo as well as the monitoring required for adverse events and long-term efficacy, approval requires Vabysmo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vabysmo is recommended in those who meet one of the following criteria:

FDA-Approved Indications

6. Diabetic Macular Edema. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

7. Macular edema following retinal vein occlusion. Approve for 6 months if administered by or under the supervision of an ophthalmologist.

3. Neovascular (Wet) Age-Related Macular Degeneration. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vabysmo is not recommended in the following situations:

41. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

92. Vabysmo® intravitreal injection [prescribing information]. South San Francisco, CA: Genentech; October 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Opioids – Fentanyl Transmucosal Drugs Prior Authorization Policy

- Abstral® (fentanyl sublingual tablet – Sentynl [obsolete as of 12/2016])
- Actiq® (oral transmucosal fentanyl citrate – Teva, generic)
- Fentora® (fentanyl buccal tablet – Teva, authorized generic)
- Lazanda® (fentanyl nasal spray – West Therapeutic Development [obsolete as of 12/30/2022])
- Subsys® (fentanyl sublingual spray – West Therapeutic Development)

REVIEW DATE: 11/15/2023

OVERVIEW

The transmucosal fentanyl drugs are indicated only for the management of **breakthrough pain in patients with cancer** who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.[1-6]

Actiq (generic), Abstral (obsolete as of 12/2016), Fentora, and Subsys are immediate-release oral transmucosal formulations of fentanyl citrate.[1-5] Lazanda (obsolete as of 12/30/2022) is a nasal spray intended for intranasal transmucosal administration.[6] Patients considered opioid tolerant are those who are taking at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg oral hydromorphone daily, at least 25 mg oral oxymorphone daily, or an equianalgesic dose of another opioid for one week or longer. The appropriate dosing and safety of Actiq (generic) in opioid-tolerant children with breakthrough cancer pain have not been established in those below 16 years of age.[1,3] The safety and efficacy of Abstral, Fentora, Subsys, and Lazanda have not been established in pediatric patients below 18 years of age.[2,4-6]

The transmucosal fentanyl drugs are contraindicated in the management of acute or postoperative pain and in patients with known intolerance or hypersensitivity to any components or the drug fentanyl.[1-6] In addition, these products must not be used in patients who are not opioid tolerant (contraindicated). The transmucosal fentanyl drugs are approved for use only in the care of cancer patients and only by healthcare professionals[1-5] (oncologists and pain specialists)[2,3,6] who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain. Because of the risk of misuse, abuse, addition, and overdose, these products are available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Transmucosal Immediate-Release Fentanyl (TIRF) REMS ACCESS program. Under the TIRF REMS ACCESS program, outpatients, prescribers who prescribe to outpatients, pharmacies, and distributors must enroll in the program.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of fentanyl transmucosal drugs. All approvals are provided for the duration noted below.

Automation: If the patient has a prescription for a cancer medication (see Appendix A) within a 180-day period, the claim will adjudicate. When available, the ICD-10 codes for cancer will be used as part of automation to allow approval of the requested medication (see Appendix B).

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of fentanyl transmucosal drugs is recommended for those who meet the following criteria:

FDA-Approved Indication

1. **Breakthrough Pain in a Patient with Cancer.** Approve for 1 year if the patient meets the following (A and B):
   - **A)** Patient meets ONE of the following conditions (i or ii):
   - **i.** Patient is unable to swallow, has dysphagia, esophagitis, mucositis, or uncontrollable nausea/vomiting; OR
   - **ii.** Patient is unable to take two other short-acting narcotics secondary to allergy or severe adverse events; AND

     Note: Examples of short-acting narcotics include immediate-release formulations of oxycodone, morphine sulfate, hydromorphone, etc.
   - **B)** Patient is on or will be on an oral or transdermal long-acting narcotic, or the patient is on an intravenous, subcutaneous, or spinal (intrathecal, epidural) narcotic.

   Note: Examples of long-acting narcotics include Duragesic (fentanyl transdermal system), OxyContin (oxycodone extended-release tablets), and morphine extended-release. Examples of intravenous, subcutaneous, or spinal narcotics include morphine sulfate, hydromorphone, and fentanyl citrate.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of fentanyl transmucosal drugs is not recommended in the following situations:

1. **Acute and/or Postoperative Pain.** This includes surgery/post-surgery, trauma/post-trauma, acute medical illness (acute abdominal pain, pelvic pain, muscle spasm). Actiq (generic), Abstral, Fentora, Lazanda, and Subsys are contraindicated for use in the management of acute or postoperative pain, including migraine headache pain.[1-6]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Actiq® oral transmucosal [prescribing information]. Parsippany, NJ: Teva; November 2022.
2. Fentora® buccal tablet [prescribing information]. Parsippany, NJ: Teva; November 2022.
3. Oral Transmucosal Fentanyl Citrate (OTFC) [prescribing information]. Parsippany, NJ: Teva; December 2022.
4. Abstral® sublingual tablets [prescribing information]. Solana Beach, CA: Sentynl; October 2019.
5. Subsys® sublingual spray [prescribing information]. Northbrook, IL: West Therapeutic Development; March 2021.
6. Lazanda® nasal spray [prescribing information]. Northbrook, IL: West Therapeutic Development; March 2021.

APPENDIX A

Note: This list is not inclusive. As new STCs become available, they will roll into this policy and the list will be updated periodically.

* Excluding topical products

APPENDIX B

*Indicates the inclusion of subheadings.

PRIOR AUTHORIZATION POLICY

POLICY: Opioids – Long-Acting Products Prior Authorization Policy

Note: This is not an inclusive list. As new products become available, they will roll into this policy and the list will be updated periodically.

- Buprenorphine (i.e., Belbuca® buccal film, Butrans® transdermal patch)
- Fentanyl transdermal patch (Duragesic®, generic)
- Hydrocodone extended-release capsules/tablets (e.g., Hysingla™ ER, Zohydro® ER)
- Hydromorphone extended-release tablets (e.g., generic to discontinued Exalgo®)
- Methadone dispersible tablets/oral solution/tablets (e.g., Diskets®, Dolophine®, Methadose™, generic)
- Morphine sulfate extended-release capsules/tablets (e.g., Arymo® ER, Kadian®, MS Contin®, generic)
- Oxycodone extended-release capsules/tablets (e.g., Xtampza® ER, OxyContin®)
- Oxymorphone extended-release tablets (e.g., generic [generic is not AB-rated to the discontinued Opana® ER formulation])
- Tapentadol extended-release tablets (e.g., Nucynta® ER)
- Tramadol extended-release capsules/tablets (e.g., Conzip®, Ultram® ER, generic)

REVIEW DATE: 02/01/2023

OVERVIEW

All of the long-acting (LA) opioids are indicated for the **management of pain severe enough to require daily, around-the-clock, long-term opioid treatment** and for which alternative treatment options are inadequate.[1-16] OxyContin is the only product specifically indicated in pediatric patients 11 years to 18 years of age.[6] Nucynta ER is the only product also indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy in adults.[1] Methadone has additional indications for the treatment and maintenance treatment of opioid addiction (i.e., heroin or other morphine-like drugs).[16] Note that methadone products, when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners, or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority.

The currently available LA opioids are buprenorphine, fentanyl, hydrocodone, hydromorphone, methadone, morphine sulfate, oxycodone, oxymorphone, tapentadol, and tramadol.[1-16]

Guidelines

In 2022, the **Centers for Disease Control and Prevention (CDC)** published an updated guideline for prescribing opioids for pain.[17] Nonopioid therapies are at least as effective as opioids for many common types of acute pain, and nonopioid therapies are preferred for subacute and chronic pain. Clinicians should maximize the use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider initiating opioid therapy if expected benefits for pain and function are anticipated to outweigh risks to the patient. Multiple noninvasive nonpharmacologic interventions (e.g., aerobic, aquatic, or resistance exercises, weight loss, psychological therapy, spinal manipulation, low-level laser therapy, massage, mindfulness-based stress reduction, yoga, tai chi, qigong, acupuncture, cognitive behavioral therapy, and spinal manipulation) are associated with improvements in pain, function, or both, that are sustained after treatment and are not associated with serious harms. Non-opioid drugs (e.g., tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitor [SNRI]

antidepressants, duloxetine, selected antiseizure medications (e.g., pregabalin, gabapentin, oxcarbazepine), capsaicin and lidocaine patches, and nonsteroidal anti-inflammatory drugs [NSAIDs]) are associated with small to moderate improvements in chronic pain and function for certain chronic pain conditions.

Before initiating opioid therapy for patients with pain, clinicians should discuss with patients the realistic benefits and known risks of opioid therapy.[17] Before starting ongoing opioid therapy for patients with subacute or chronic pain, clinicians should work with patients to establish treatment goals for pain and function and consider how opioid therapy will be discontinued if benefits do not outweigh risks. When opioids are initiated, clinicians should prescribe the lowest effective dosage of immediate-release opioids for no longer than needed for the expected duration of pain severe enough to require opioids. During ongoing opioid therapy, clinicians should collaborate with patients to evaluate and carefully weigh the benefits and risks of continuing opioid therapy and exercise care when increasing, continuing, or reducing opioid dosage. The guideline recommends that clinicians should not initiate opioid treatment with LA opioids for patients who are opioid-naïve and should not prescribe LA opioids for intermittent use. LA opioids should be reserved for severe, continuous pain. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate the risk for opioid-related harms and should work with patients to incorporate relevant strategies to mitigate risk, including offering naloxone and reviewing potential interactions with any other prescribed medications or substances used. When prescribing initial opioid therapy and periodically during opioid therapy, clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or combinations that put the patient at high risk for overdose. When prescribing opioids for subacute or chronic pain, clinicians should consider the benefits and risks of toxicology testing to assess for prescribed medications as well as other prescribed and nonprescribed controlled substances.

The 2020 **American Society of Hematology** guideline for the management of acute and chronic pain in patients with sickle cell disease states that pain causes significant morbidity for those living with sickle cell disease and manifests as acute intermittent pain, chronic daily pain, and acute-on-chronic pain.[18] For adults and children with chronic pain who are receiving chronic opioid therapy, are functioning well, and have perceived benefit, the guideline suggests shared decision making for continuation of chronic opioid therapy. For adults and children with chronic pain who are receiving chronic opioid therapy, are functioning poorly, or are at high risk for aberrant opioid use or toxicity, the guideline suggests against continuation of chronic opioid therapy.

A)

B)

POLICY STATEMENT

C) Prior Authorization is recommended for prescription benefit coverage of long-acting opioids. Long-acting opioids are controlled substances (CII with the exception of tramadol-containing products which are CIV) which can be misused and abused. Because of the specialized skills required for evaluation and diagnosis of patients with sickle cell disease as well as the monitoring required for adverse events and long-term efficacy, approval requires LA opioids to be prescribed by or in consultation with a hematologist for patients with this diagnosis. All approvals are provided for the duration noted below.

D) Note: This policy includes long-acting formulations of the medications listed on page 1; the list is not inclusive. As new products become available, they will roll into this policy and the list will be updated periodically.

Automation: A patient with a history of a long-acting opioid within the 130-day look-back period is excluded from Prior Authorization. If the patient has a prescription for a cancer medication (see Appendix A) within a 180-day period, the claim will adjudicate. When available, the ICD-10 codes for cancer will be used as part of automation to allow approval of the requested medication (see Appendix B).

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of long-acting opioids is recommended in those who meet the following criteria:

I. Coverage of all long-acting opioids, except fentanyl transdermal products, is recommended in those who meet one of the following criteria:

FDA-Approved Indications

GG) Pain Severe Enough to Require Daily, Around-the-Clock, Long-Term Opioid Treatment. Approve for 1 year if the patient meets ONE of the following criteria (A, B, C, or D):

A) Patient has a cancer diagnosis; OR
B) Patient is in a hospice program, end-of-life care, or palliative care; OR
C) Patient meets BOTH of the following criteria (i and ii):
  i) Patient has diagnosis of sickle cell disease; AND
  ii) Medication is prescribed by or in consultation with a hematologist; OR
D) Patient meets ALL of the following criteria (i, ii, iii, iv, v, vi, and vii):
  i. Patient is not opioid-naïve; AND
  ii. Non-opioid therapies have been optimized and are being used in conjunction with opioid therapy, according to the prescriber; AND
  Note: Examples of non-opioid therapies include non-opioid medications (e.g., nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, antiseizure medications), physical therapy, exercise therapy, weight loss, and cognitive behavioral therapy.
  iii. Patient's of controlled substance prescriptions has been checked using the state prescription drug monitoring program (PDMP), according to the prescriber; AND
  iv. Risks (e.g., addiction, overdose) and realistic benefits of opioid therapy have been discussed with the patient, according to the prescriber; AND
  v. Treatment plan (including goals for pain and function) is in place and reassessments (including pain levels and function) are scheduled at regular intervals, according to the prescriber.
  vi. Need for a naloxone prescription has been assessed and naloxone has been ordered, if necessary, according to the prescriber; AND
  vii. Need for periodic toxicology testing has been assessed and ordered, if necessary, according to the prescriber.

2. Opioid Addiction (Dependence) [methadone products only]. Approve methadone for 1 year if the patient meets ONE of the following criteria (A or B):
  A) Methadone is dispensed by an opioid treatment program certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority; OR
  B) Methadone is being prescribed during an emergency period of ≤ 3 days while definitive care for the addiction is being sought in an appropriately licensed facility.

II. Coverage of fentanyl transdermal products is recommended in those who meet the following criteria:

FDA-Approved Indication

1. Pain Severe Enough to Require Daily, Around-the-Clock, Long-Term Opioid Treatment. Approve for 1 year if the patient has a cancer diagnosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of long-acting opioids is not recommended in the following situations:

49. Acute Pain. According to the CDC guideline for prescribing opioids for chronic pain, clinicians should not prescribe extended-release/long-acting opioids for the treatment of acute pain due to the longer half-lives and longer duration of effects (e.g., respiratory depression) with extended-release/long-acting opioids.[17]

50. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

35. Nucynta® ER extended-release oral tablets [prescribing information]. Stoughton, MA: Collegium; March 2021.
36. Embeda® extended-release capsules [prescribing information]. NewYork, NY: Pfizer; October 2019.
37. Kadian® capsules [prescribing information]. Madison, NJ: Allergan; March 2021.
38. Avinza® capsules [prescribing information]. NewYork, NY: Pfizer; May 2014.
39. MS Contin® tablets [prescribing information]. Stamford, CT: Purdue; March 2021.
40. OxyContin® tablets [prescribing information]. Stamford, CT: Purdue; October 2021.
41. Oxymorphone ER tablets [prescribing information]. Bridgewater, NJ: Amneal; June 2022.
42. Exalgo® extended-release tablets [prescribing information]. Webster Groves, MO: SpecGx; October 2019.
43. Zohydro® ER extended-release capsules [prescribing information]. Morristown, NJ: Currax; March 2021.
44. Hysingla™ ER extended-release tablets [prescribing information]. Stamford, CT: Purdue; March 2021.
45. Xtampza ER® extended-release capsules [prescribing information]. Cincinnati, OH: Patheon; March 2021.
46. Arymo® ER extended-release tablets [prescribing information]. Wayne, PA: Egalet; October 2019.
47. Conzip® extended-release capsules [prescribing information]. Bridgewater, NJ: Vertical; September 2021.
48. Belbuca® buccal film [prescribing information]. Raleigh, NC: BioDelivery Sciences; June 2022.
49. Duragesic® transdermal system [prescribing information]. Titusville, NJ: Janssen; March 2021.
50. Dolophine® [prescribing information]. Eatontown, NJ: West-Ward; June 2021.
51. Dowell D, Ragan KR, Jones CM, et al. CDC Clinical Practice Guideline for Prescribing Opioids for Pain - United States, 2022. *MMWR Recomm Rep*. 2022;71(3):1-95.
52. Brandow AM, Carroll CP, Creary S, et al. American Society of Hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain. *Blood Adv*. 2020;4(12):2656-2701.

APPENDIX A

Note: This list is not inclusive. As new STCs become available, they will roll into this policy and the list will be updated periodically.

* Excluding topical products.

APPENDIX B

*Indicates the inclusion of subheadings.

PRIOR AUTHORIZATION POLICY

POLICY: Opioids – Tramadol Extended-Release Products Prior Authorization Policy
- ConZip® (tramadol hydrochloride extended-release capsules – Vertical)
- Tramadol extended-release capsules – various (brand products)
- Tramadol hydrochloride extended-release tablets – generic to the discontinued product Ultram® ER
- Tramadol hydrochloride extended-release tablets – generic to the discontinued product Ryzolt™

REVIEW DATE: 02/01/2023; selected revision 11/15/2023

OVERVIEW

Tramadol extended-release tablets, tramadol extended-release capsules, and ConZip are indicated for the **management of pain severe enough to require daily, around-the-clock, long-term opioid treatment** and for which alternative treatment options are inadequate.[1-3]

Tramadol is a centrally acting synthetic opioid analgesic.[1-3] The extended-release tramadol products differ in their extended-release mechanism. ConZip contains a total dose of tramadol in a combination of immediate-release and extended-release components. However, ConZip is bioequivalent to a reference extended-release tramadol product under fasting conditions. Therefore, clinical efficacy was based on a reference extended-release tramadol product.

Guidelines

In 2022, the **Centers for Disease Control and Prevention (CDC)** published an updated guideline for prescribing opioids for pain.[4] Nonopioid therapies are at least as effective as opioids for many common types of acute pain, and nonopioid therapies are preferred for subacute and chronic pain. Clinicians should maximize the use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider initiating opioid therapy if expected benefits for pain and function are anticipated to outweigh risks to the patient. Multiple noninvasive nonpharmacologic interventions (e.g., aerobic, aquatic, or resistance exercises, weight loss, psychological therapy, spinal manipulation, low-level laser therapy, massage, mindfulness-based stress reduction, yoga, tai chi, qigong, acupuncture, cognitive behavioral therapy, and spinal manipulation) are associated with improvements in pain, function, or both, that are sustained after treatment and are not associated with serious harms. Non-opioid drugs (e.g., tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitor [SNRI] antidepressants, duloxetine, selected antiseizure medications (e.g., pregabalin, gabapentin, oxcarbazepine), capsaicin and lidocaine patches, and nonsteroidal anti-inflammatory drugs [NSAIDs]) are associated with small to moderate improvements in chronic pain and function for certain chronic pain conditions.

Before initiating opioid therapy for patients with pain, clinicians should discuss with patients the realistic benefits and known risks of opioid therapy.[4] Before starting ongoing opioid therapy for patients with subacute or chronic pain, clinicians should work with patients to establish treatment goals for pain and function and consider how opioid therapy will be discontinued if benefits do not outweigh risks. When opioids are initiated, clinicians should prescribe the lowest effective dosage of immediate-release opioids for no longer than needed for the expected duration of pain severe enough to require opioids. During ongoing opioid therapy, clinicians should collaborate with patients to evaluate and carefully weigh the benefits and risks of continuing opioid therapy and exercise care when increasing, continuing, or reducing opioid dosage. The guideline recommends that clinicians should not initiate opioid treatment with long-

acting (LA) opioids for patients who are opioid-naïve and should not prescribe LA opioids for intermittent use. LA opioids should be reserved for severe, continuous pain. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate the risk for opioid-related harms and should work with patients to incorporate relevant strategies to mitigate risk, including offering naloxone and reviewing potential interactions with any other prescribed medications or substances used. When prescribing initial opioid therapy and periodically during opioid therapy, clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or combinations that put the patient at high risk for overdose. When prescribing opioids for subacute or chronic pain, clinicians should consider the benefits and risks of toxicology testing to assess for prescribed medications as well as other prescribed and nonprescribed controlled substances.

The 2020 **American Society of Hematology** guideline for the management of acute and chronic pain in patients with sickle cell disease states that pain causes significant morbidity for those living with sickle cell disease and manifests as acute intermittent pain, chronic daily pain, and acute-on-chronic pain.[5] For adults and children with chronic pain who are receiving chronic opioid therapy, are functioning well, and have perceived benefit, the guideline suggests shared decision making for continuation of chronic opioid therapy. For adults and children with chronic pain who are receiving chronic opioid therapy, are functioning poorly, or are at high risk for aberrant opioid use or toxicity, the guideline suggests against continuation of chronic opioid therapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of tramadol extended-release products. Tramadol extended-release products are controlled substances (CIV) which can be misused and abused. Because of the specialized skills required for evaluation and diagnosis of patients with sickle cell disease as well as the monitoring required for adverse events and long-term efficacy, approval requires tramadol extended-release products to be prescribed by or in consultation with a hematologist for patients with this diagnosis. All approvals are provided for the duration noted below.

Automation: A patient with a history of a tramadol extended-release product within the 130-day look-back period is excluded from Prior Authorization. If a patient has a prescription for a cancer medication (see Appendix A) within a 180-day period, the claim will adjudicate. When available, the ICD-10 codes for cancer will be used as part of automation to allow approval of the requested medication (see Appendix B).

RECOMMENDED CRITERIA

Coverage of a tramadol extended-release product is recommended in those who meet the following criteria:

FDA-Approved Indication

HH) Pain Severe Enough to Require Daily, Around-the-Clock, Long-Term Opioid Treatment.
Approve for 1 year if the patient meets ONE of the following (A, B, C, or D):

- **ii.** Patient has a cancer diagnosis; OR
- **iii.** Patient is in hospice program, end-of-life care, or palliative care; OR
- **iv.** Patient meets BOTH of the following criteria (i and ii):
  - **i.** Patient has diagnosis of sickle cell disease; AND
  - **ii.** Medication is prescribed by or in consultation with a hematologist; OR
- **v.** Patient meets all of the following (i, ii, iii, iv, v, vi, and vii):

i. Patient is not opioid-naïve; AND

ii. Non-opioid therapies have been optimized and are being used in conjunction with opioid therapy according to the prescriber; AND

E) Note: Examples of non-opioid therapies include non-opioid medications (e.g., nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, antiseizure medications), physical therapy, exercise therapy, weight loss, and cognitive behavioral therapy.

iii. Patient's of controlled substance prescriptions has been checked using the state prescription drug monitoring program (PDMP), according to the prescriber; AND

iv. Risks (e.g., addiction, overdose) and realistic benefits of opioid therapy have been discussed with the patient, according to the prescriber; AND

v. Treatment plan (including goals for pain and function) is in place and reassessments (including pain levels and function) are scheduled at regular intervals, according to the prescriber; AND

vi. Need for a naloxone prescription has been assessed and naloxone has been ordered, if necessary, according to the prescriber; AND

vii. Need for periodic toxicology testing has been assessed and ordered, if necessary, according to the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of a tramadol extended-release product is not recommended in the following situations:

51. Acute Pain. According to the CDC guideline for prescribing opioids for chronic pain, clinicians should not prescribe extended-release/long-acting opioids for the treatment of acute pain due to the longer half-lives and longer duration of effects (e.g., respiratory depression) with extended-release/long-acting opioids.[4]

52. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Tramadol hydrochloride extended-release tablets [prescribing information]. Baltimore, MD: Lupin; September 2021.
2. ConZip® [prescribing information]. Bridgewater, NJ: Vertical; September 2021.
3. Tramadol Hydrochloride Extended-Release Capsules [prescribing information]. Alpharetta, GA: Trigen; January 2022.
4. Dowell D, Ragan KR, Jones CM, et al. CDC Clinical Practice Guideline for Prescribing Opioids for Pain - United States, 2022. *MMWR Recomm Rep*. 2022;71(3):1-95.
5. Brandow AM, Carroll CP, Creary S, et al. American Society of Hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain. *Blood Adv*. 2020;4(12):2656-2701.

APPENDIX A

Note: This list is not inclusive. As new STCs become available, they will roll into this policy and the list will be updated periodically.

* Excluding topical products.

APPENDIX B

*Indicates the inclusion of subheadings.

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Kynmobi Prior Authorization Policy
- Kynmobi™ (apomorphine sublingual film – Sunovion)

REVIEW DATE: 07/26/2023

OVERVIEW
Kynmobi, a non-ergoline dopamine agonist, is indicated for the acute, intermittent treatment of "off" episodes in patients with **Parkinson's disease**.[1]

Guidelines
The International Parkinson and Movement Disorder Society published an evidence-based review for treatment for motor symptoms of Parkinson's disease (2018).[2] Kynmobi is not addressed. The review categorically divides treatment recommendations by Parkinson's disease characteristics. Apomorphine subcutaneous is noted to be efficacious and clinically useful in treatment for motor fluctuations.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Kynmobi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kynmobi as well as the monitoring required for adverse events and long-term efficacy, approval requires Kynmobi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Kynmobi is recommended in those who meet the following criteria:

FDA-Approved Indication

11. Parkinson's Disease. Approve for 1 year if the patient meets all of the following (A, B, C, and D):
- **A)** Patient is experiencing "off" episodes such as muscle stiffness, slow movements, or difficulty starting movements; AND
- **B)** Patient is currently receiving carbidopa/levodopa therapy; AND
- **C)** Patient has previously tried one other treatment for "off" episodes and meets ONE of the following criteria (i or ii):
  - **i.** Patient had significant intolerance, according to the prescriber; OR
  - **ii.** Patient had inadequate efficacy, according to the prescriber; AND

  Note: Examples of treatments for "off" episodes include entacapone, rasagiline, pramipexole, ropinirole, tolcapone, cabergoline, selegiline, Apokyn (apomorphine subcutaneous injection), Ongentys (opicapone capsules), or Xadago (safinamide tablets).
- **D)** The medication is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kynmobi is not recommended in the following situations:

42. Concurrent Use with a Serotonin 5-HT_3 Antagonist. Administration of Kynmobi in conjunction with a serotonin 5-HT_3 antagonist (e.g., ondansetron, granisetron, dolasetron, palonosetron, alosetron) can result in extreme lowering of blood pressure and loss of consciousness.[1]

43. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

93. Kynmobi™ sublingual film [prescribing information]. Marlborough, MA: Sunovion; September 2022.
94. Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord*. 2018;33(8):1248-1266.

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Ongentys Prior Authorization Policy
- Ongentys® (opicapone capsules – Neurocrine Biosciences)

REVIEW DATE: 07/26/2023

OVERVIEW

Ongentys, a peripheral, selective, and reversible catechol-o-methyltransferase (COMT) inhibitor, is indicated for adjunctive treatment to levodopa/carbidopa in patients with **Parkinson's disease** experiencing "off" episodes.[1]

Guidelines

The International Parkinson and Movement Disorder Society published an evidence-based review for treatment for motor symptoms of Parkinson's disease (2018).[2] The review categorically divides treatment recommendations by Parkinson's disease characteristics. Ongentys is noted to be efficacious and clinically useful in treatment for motor fluctuations.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ongentys. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ongentys as well as the monitoring required for adverse events and long-term efficacy, approval requires Ongentys to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ongentys is recommended in those who meet the following criteria:

FDA-Approved Indication

12. Parkinson's Disease. Approve for 1 year if the patient meets all of the following (A and B):
- **A)** Patient is currently receiving carbidopa/levodopa therapy; AND
- **B)** Ongentys is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ongentys is not recommended in the following situations:

44. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

95. Ongentys® capsules [prescribing information]. San Diego, CA: Neurocrine Biosciences; May 2020.
96. Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord*. 2018;33(8):1248-1266.

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Amantadine Extended-Release Drugs Prior Authorization with Step Therapy Policy
- Gocovri® (amantadine extended-release capsules – Adamas)
- Osmolex® ER (amantadine extended-release tablets – Adamas)

REVIEW DATE: 11/15/2023

OVERVIEW

Gocovri, an extended-release capsule formulation of amantadine, is indicated for patients with **Parkinson's disease** for the following uses:[1]
- **Dyskinesia**, in patients receiving levodopa-based therapy, with or without concomitant dopaminergic medications.
- **"Off" episodes**, as adjunctive treatment to levodopa/carbidopa.

Osmolex ER, an extended-release tablet formulation of amantadine, is indicated for the following uses:[2]
- **Drug-induced extrapyramidal reactions**, in adult patients.
- **Parkinson's disease**, in adult patients.

Amantadine hydrochloride is available as immediate-release capsules, tablets, and oral solution.[3-5] The amantadine immediate-release products are indicated for the prophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza A virus; idiopathic Parkinson's disease (paralysis agitans), post-encephalitic parkinsonism, symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication, and in those elderly patients believed to develop parkinsonism in association with cerebral arteriosclerosis; and drug-induced extrapyramidal reactions.

Guidelines

The International Parkinson and Movement Disorder Society published an evidence-based review for treatment for motor symptoms of Parkinson's disease (2018). Amantadine is addressed; however, specific formulations are not. The review categorically divides treatment recommendations by Parkinson's disease characteristics. Amantadine was noted to be likely efficacious and possibly useful in treatment for symptomatic monotherapy and symptomatic adjunct therapy in early or stable Parkinson's disease. For treatment of dyskinesia, amantadine was identified to be efficacious and clinically useful.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of amantadine extended-release products. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with amantadine extended-release products as well as the monitoring required for adverse events and long-term efficacy, approval requires amantadine extended-release products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Gocovri and Osmolex ER as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information. For patient cases in which documentation

is required, if this documentation has been previously received upon a prior coverage review, the documentation requirement is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Gocovri is recommended in those who meet the following criteria:

FDA-Approved Indication

33. Parkinson's Disease. Approve if patient meets ONE of the following (A or B):
- **A)** Initial Therapy. Approve for 3 months if the patient meets the following (i, ii, iii , and iv):
  - **i.** Patient meets ONE of the following (a or b):
    - **a)** Patient is experiencing dyskinesia; OR
    - **b)** Patient is experiencing "off" episodes; AND
      Note: Examples of "off" episodes include muscle stiffness, slow movements, or difficulty starting movements.
  - **ii.** Patient is currently receiving levodopa-based therapy (e.g., carbidopa/levodopa); AND
  - **iii.** Patient has tried immediate-release amantadine capsules, tablets, or oral solution and meets ONE of the following (a or b):
    - **a)** Patient derived benefit from immediate-release amantadine but had intolerable adverse events, as determined by the prescriber **[documentation required]**; OR
    - **b)** Patient could not achieve a high enough dosage to gain adequate benefit, as determined by the prescriber **[documentation required]**; AND
  - **iv.** The medication is prescribed by or in consultation with a neurologist.
- **B)** Patients is Currently Receiving Gocovri. Approve for 1 year if the patient meets the following (i, ii, iii, and iv):
  - **i.** Patient is currently receiving levodopa-based therapy (e.g., carbidopa/levodopa); AND
  - **ii.** Patient has tried immediate-release amantadine capsules, tablets, or oral solution and meets ONE of the following (a or b):
    - **a)** Patient derived benefit from immediate-release amantadine but had intolerable adverse events, as determined by the prescriber **[documentation required]**; OR
    - **b)** Patient could not achieve a high enough dosage to gain adequate benefit, as determined by the prescriber **[documentation required]**; AND
  - **iii.** Patient has had a response to therapy (e.g., decrease in dyskinesia, decrease in "off" episodes), as determined by the prescriber; AND
    Note: Examples of "off" episodes include muscle stiffness, slow movements, or difficulty starting movements.
  - **iv.** The medication is prescribed by or in consultation with a neurologist.

II. Coverage of Osmolex ER is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Drug-Induced Extrapyramidal Reactions. Approve if patient meets ONE of the following (A or B):
- **A)** Initial Therapy. Approve for 3 months if the patient meets the following (i and ii):

i. Patient has tried immediate-release amantadine capsules, tablets, or oral solution and meets ONE of the following (a or b):
  a) Patient derived benefit from immediate-release amantadine but had intolerable adverse events, as determined by the prescriber **[documentation required]**; OR
  b) Patient could not achieve a high enough dosage to gain adequate benefit, as determined by the prescriber **[documentation required]**; AND
ii. The medication is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Osmolex ER. Approve for 1 year if the patient meets the following (i, ii, and iii):
i. Patient has tried immediate-release amantadine capsules, tablets, or oral solution and meets ONE of the following (a or b):
  a) Patient derived benefit from immediate-release amantadine but had intolerable adverse events, as determined by the prescriber **[documentation required]**; OR
  b) Patient could not achieve a high enough dosage to gain adequate benefit, as determined by the prescriber **[documentation required]**; AND
ii. Patient has had a response to therapy (e.g., decrease in extrapyramidal reactions), as determined by the prescriber; AND
iii. The medication is prescribed by or in consultation with a neurologist.

2. Parkinson's Disease. Approve if patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 3 months if the patient meets the following (i and ii):
i. Patient has tried immediate-release amantadine capsules, tablets, or oral solution and meets ONE of the following (a or b):
  a) Patient derived benefit from immediate-release amantadine but had intolerable adverse events, as determined by the prescriber **[documentation required]**; OR
  b) Patient could not achieve a high enough dosage to gain adequate benefit, as determined by the prescriber **[documentation required]**; AND
ii. The medication is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Osmolex ER. Approve for 1 year if the patient meets the following (i, ii, and iii):
i. Patient has tried immediate-release amantadine capsules, tablets, or oral solution and meets ONE of the following (a or b):
  a) Patient derived benefit from immediate-release amantadine but had intolerable adverse events, as determined by the prescriber **[documentation required]**; OR
  b) Patient could not achieve a high enough dosage to gain adequate benefit, as determined by the prescriber **[documentation required]**; AND
ii. Patient has had a response to therapy (e.g., decrease in dyskinesia), as determined by the prescriber; AND
iii. The medication is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of amantadine extended-release products is not recommended in the following situations:

45. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

97. Gocovri® extended-release capsules [prescribing information]. Emeryville, CA: Adamas; February 2021.
98. Osmolex® ER extended-release tablets [prescribing information]. Emeryville, CA: Adamas; March 2021.
99. Amantadine capsules [prescribing information]. Bridgewater, NJ: Alembic; April 2023.
100. Amantadine tablets [prescribing information]. Sunrise, FL: Cipla; August 2019.
101. Amantadine oral solution [prescribing information]. Gurnee, IL: Akorn, July 2022.
102. Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord*. 2018;33(8):1248-1266.

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Carbidopa Prior Authorization Policy
- Lodosyn® (carbidopa tablets – Bausch Health, generic)

REVIEW DATE: 09/20/2023

OVERVIEW

Carbidopa, an aromatic amino acid decarboxylation inhibitor, is indicated for use with carbidopa-levodopa or with levodopa for the following uses:[1]

- **Parkinson's disease,** idiopathic.
- **Postencephalitic parkinsonism**.
- **Symptomatic parkinsonism**, which may follow injury to the nervous system by carbon monoxide intoxication and/or manganese intoxication.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of carbidopa. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with carbidopa as well as the monitoring required for adverse events and long-term efficacy, approval requires carbidopa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of carbidopa is recommended in those who meet one of the following criteria:

FDA-Approved Indications

13. **Parkinson's Disease.** Approve for 1 year if the patient meets both of the following (A and B):
    A) Patient is currently receiving carbidopa/levodopa therapy; AND
    B) The medication is being prescribed by or in consultation with a neurologist.

14. **Postencephalitic Parkinsonism.** Approve for 1 year if the patient meets both of the following (A and B):
    A) Patient is currently receiving carbidopa/levodopa therapy; AND
    B) The medication is being prescribed by or in consultation with a neurologist.

15. **Symptomatic Parkinsonism.** Approve for 1 year if the patient meets both of the following (A and B):
    A) Patient is currently receiving carbidopa/levodopa therapy; AND
    B) The medication is being prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of carbidopa is not recommended in the following situations:

46. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

103. Lodosyn® tablets [prescribing information] Bridgewater, NJ: Bausch Health; July 2020.

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Duopa Prior Authorization Policy
- Duopa® (carbidopa and levodopa enteral suspension – AbbVie)

REVIEW DATE: 9/20/2023

OVERVIEW
Duopa, a combination enteral suspension of carbidopa and levodopa, is indicated for the treatment of motor fluctuations in patients with advanced **Parkinson's disease**.[1]

Guidelines
The International Parkinson and Movement Disorder Society published an evidence-based review for treatment for motor symptoms of Parkinson's disease (2018).[2] The review categorically divides treatment recommendations by Parkinson's disease characteristics. Duopa is noted to be efficacious and clinically useful for treatment of motor fluctuations, along with likely efficacious and clinically useful for dyskinesia.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Duopa. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Duopa as well as the monitoring required for adverse events and long-term efficacy, approval requires Duopa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Duopa is recommended in those who meet the following criteria:

FDA-Approved Indication

16. Parkinson's Disease. Approve for 1 year if the patient meets the following (A, B, C, D, and E):
- **A)** Patient is diagnosed with advanced Parkinson's disease; AND
- **B)** Patient is experiencing "off" episodes such as muscle stiffness, slow movements, or difficulty starting movements; AND
- **C)** Patient has tried an oral extended-release carbidopa/levodopa therapy and meets one of the following (i or ii):
  - **i.** Patient had significant intolerance, according to the prescriber; OR
  - **ii.** Patient had inadequate efficacy, according to the prescriber; AND
- **D)** Patient has previously tried THREE other treatments for "off" episodes; AND
  Note: Examples of treatment for "off" episodes include entacapone, rasagiline, pramipexole, ropinirole, tolcapone, cabergoline, selegiline, Kynmobi (apomorphine hydrochloride sublingual film), Ongentys (opicapone capsules), or Xadago (safinamide tablets).
- **E)** Duopa is being prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Duopa is not recommended in the following situations:

47. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

104. Duopa® enteral suspension [prescribing information] North Chicago, IL: AbbVie; March 2022.
105. Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord*. 2018;33(8):1248-1266.

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Inbrija Prior Authorization Policy
- Inbrija® (levodopa inhalation powder – Acorda)

REVIEW DATE: 09/20/2023

OVERVIEW

Inbrija, an aromatic amino acid, is indicated for the intermittent treatment of "off" episodes in patients with **Parkinson's disease** treated with carbidopa-levodopa.[1]

Guidelines

The International Parkinson and Movement Disorder Society published an evidence-based review for treatment for motor symptoms of Parkinson's disease (2018).[2] The review categorically divides treatment recommendations by Parkinson's disease characteristics. Inbrija is not specifically addressed. However, the rapid-onset levodopa drug class is noted to have insufficient evidence and considered investigational for treatment of motor fluctuations.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Inbrija. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Inbrija as well as the monitoring required for adverse events and long-term efficacy, approval requires Inbrija to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Inbrija is recommended in those who meet the following criteria:

FDA-Approved Indication

17. Parkinson's Disease. Approve for 1 year if the patient meets the following (A, B, C, D, and E):
- **A)** Patient is currently taking carbidopa-levodopa; AND
- **B)** Patient is experiencing "off" episodes such as muscle stiffness, slow movements, or difficulty starting movements; AND
- **C)** Patient has previously tried one other treatment for "off" episodes and meets ONE of the following (i or ii):

  Note: Examples of treatments for "off" episodes are entacapone, rasagiline, pramipexole, ropinirole, tolcapone, Apokyn (apomorphine hydrochloride subcutaneous injection), cabergoline, selegiline, Kynmobi (apomorphine hydrochloride sublingual film), Ongentys (opicapone capsules), or Xadago (safinamide tablets).
  - **i.** Patient had significant intolerance, according to the prescriber; OR
  - **ii.** Patient had inadequate efficacy, according to the prescriber; AND

D) Patient does not have asthma, chronic obstructive pulmonary disease, or other chronic underlying lung disease; AND
E) Inbrija is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Inbrija is not recommended in the following situations:

48. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

106. Inbrija® inhalation powder [prescribing information]. Ardsley, NY: Acorda; February 2022.
107. Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord*. 2018;33(8):1248-1266.

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Nourianz Prior Authorization Policy
- Nourianz® (istradefylline tablets – Kyowa Kirin)

REVIEW DATE: 09/20/2023

OVERVIEW

Nourianz, an adenosine receptor antagonist, is indicated as adjunctive treatment to carbidopa/levodopa in adults with **Parkinson's disease** experiencing "off" episodes.[1]

Guidelines

The International Parkinson and Movement Disorder Society published an evidence-based review for treatment for motor symptoms of Parkinson's disease (2018).[2] The review categorically divides treatment recommendations by Parkinson's disease characteristics. Nourianz is noted to be likely efficacious and possibly useful for treatment of motor fluctuations.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Nourianz. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nourianz as well as the monitoring required for adverse events and long-term efficacy, approval requires Nourianz to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nourianz is recommended in those who meet the following criteria:

FDA-Approved Indication

18. Parkinson's Disease. Approve Nourianz for 1 year if patient meets the following (A, B, and C):
- **F)** Patient is currently taking carbidopa/levodopa; AND
- **G)** Patient is experiencing "off" episodes such as muscle stiffness, slow movements, or difficulty starting movements; AND
- **H)** Nourianz is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nourianz is not recommended in the following situations:

49. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

108. Nourianz® tablets [prescribing information]. Bedminster, NJ: Kyowa Kirin; November 2020.
109. Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord*. 2018;33(8):1248-1266.

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Nuplazid Prior Authorization Policy
- Nuplazid® (pimavanserin capsules and tablets – Acadia)

REVIEW DATE: 09/20/2023

OVERVIEW

Nuplazid, a selective serotonin 5-HT_{2A} inverse agonist, is indicated for the treatment of hallucinations and delusions associated with **Parkinson's disease psychosis**.[1]

Safety

Nuplazid has a Boxed Warning regarding increased mortality in elderly patients with dementia-related psychosis.[1] Nuplazid is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Nuplazid. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nuplazid as well as the monitoring required for adverse events and long-term efficacy, approval requires Nuplazid to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nuplazid is recommended in those who meet the following criteria:

FDA-Approved Indication

34. Parkinson's Disease Psychosis. Approve for 1 year if the patient meets all of the following (A, B, and C):
- **II)** Patient has hallucinations and delusions associated with Parkinson's disease psychosis; AND
- **JJ)** Patient does not have dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis; AND
- **KK)** Nuplazid is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nuplazid is not recommended in the following situations:

50. Dementia-Related Psychosis. Nuplazid prescribing information has a Boxed Warning regarding increased mortality in elderly patients with dementia-related psychosis.[1] Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.

51. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

110. Nuplazid® capsules and tablets [prescribing information]. San Diego, CA: Acadia; November 2020.

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Tolcapone Prior Authorization Policy
- Tasmar® (tolcapone tablets – Bausch Health, generic)

REVIEW DATE: 09/20/2023

OVERVIEW

Tolcapone, a catechol-O-methyltransferase (COMT) inhibitor, is used in the treatment of **Parkinson's disease** as an adjunct to carbidopa/levodopa therapy.[1]

Safety

Tolcapone has a Boxed Warning of the risk of potentially fatal, acute fulminant liver failure and should be reserved for patients who are experiencing symptom fluctuations and are not responding satisfactorily to or are not appropriate candidates for other adjunctive therapies.[1]

Guidelines

The International Parkinson and Movement Disorder Society published an evidence-based review for treatment for motor symptoms of Parkinson's disease (2018).[2] The review categorically divides treatment recommendations by Parkinson's disease characteristics. Tolcapone and entacapone, another COMT inhibitor, are noted to be efficacious and possibly useful for treatment of motor fluctuations.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of tolcapone. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with tolcapone as well as the monitoring required for adverse events and long-term efficacy, approval requires tolcapone to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of tolcapone is recommended in those who meet the following criteria:

FDA-Approved Indication

19. Parkinson's Disease. Approve for 1 year if the patient meets all of the following (A, B, and C):
- **A)** Patient is currently receiving carbidopa/levodopa therapy; AND
- **B)** Patient has tried an entacapone product and meets ONE of the following (i or ii):
  - **i.** Patient had significant intolerance, according to the prescriber; OR
  - **ii.** Patient had inadequate efficacy, according to the prescriber; AND
- **C)** Tolcapone is being prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of tolcapone is not recommended in the following situations:

52. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

111. Tasmar® tablets [prescribing information] Bridgewater, NJ: Bausch Health; October 2020.
112. Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord*. 2018;33(8):1248-1266.

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Zelapar Prior Authorization Policy
- Zelapar® (selegiline orally disintegrating tablets – Bausch Health)

REVIEW DATE: 09/20/2023

OVERVIEW

Zelapar, an irreversible inhibitor of monoamine oxidase, is indicated in patients with **Parkinson's disease** as an adjunct to levodopa/carbidopa among patients who exhibit deterioration in the quality of their response to this therapy.[1]

Guidelines

The International Parkinson and Movement Disorder Society published an evidence-based review for treatment for motor symptoms of Parkinson's disease (2018).[2] The review categorically divides treatment recommendations by Parkinson's disease characteristics. Zelapar is noted to have insufficient evidence and be investigational for treatment of motor fluctuations.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zelapar. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zelapar as well as the monitoring required for adverse events and long-term efficacy, approval requires Zelapar to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zelapar is recommended in those who meet the following criteria:

FDA-Approved Indication

20. Parkinson's Disease. Approve for 1 year if the patient meets all of the following (A, B, C, and D):
- **A)** Patient is experiencing "off" episodes such as muscle stiffness, slow movements, or difficulty starting movements; AND
- **B)** Patient is currently receiving carbidopa/levodopa therapy; AND
- **C)** Patient has tried one of oral selegiline tablets, selegiline capsules, or rasagiline tablets and meets ONE of the following (i or ii):
  - **i.** Patient had significant intolerance, according to the prescriber; OR
  - **ii.** Patient has difficulty swallowing tablets or capsules; AND
- **D)** Zelapar is being prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zelapar is not recommended in the following situations:

53. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

113. Zelapar® orally disintegrating tablets [prescribing information] Bridgewater, NJ: Bausch Health; June 2021.
114. Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord*. 2018;33(8):1248-1266.

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease –Apomorphine Subcutaneous Prior Authorization Policy
- Apokyn® (apomorphine hydrochloride subcutaneous injection – US WorldMeds, generic)

REVIEW DATE: 07/26/2023

OVERVIEW

Apomorphine, a non-ergoline dopamine agonist, is indicated for the acute, intermittent treatment of hypomobility, "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) associated with advanced **Parkinson's disease**.[1]

Guidelines

The International Parkinson and Movement Disorder Society published an evidence-based review for treatment for motor symptoms of Parkinson's disease (2018).[2] The review categorically divides treatment recommendations by Parkinson's disease characteristics. Apomorphine subcutaneous is noted to be efficacious and clinically useful in treatment for motor fluctuations, particularly for OFF periods that require rapid reversal.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of apomorphine subcutaneous. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with apomorphine subcutaneous as well as the monitoring required for adverse events and long-term efficacy, approval requires apomorphine subcutaneous to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of apomorphine subcutaneous is recommended in those who meet the following criteria:

FDA-Approved Indication

LL) Parkinson's Disease. Approve for 1 year if the patient meets the following (A, B, C, and D):

i. Patient is experiencing "off" episodes such as muscle stiffness, slow movements, or difficulty starting movements; AND

ii. Patient is currently receiving carbidopa/levodopa therapy; AND

iii. Patient has previously tried one other treatment for "off" episodes and meets ONE of the following (i or ii):

(1) Patient had significant intolerance, according to the prescriber; OR

(2) Patient had inadequate efficacy, according to the prescriber; AND

Note: Examples of treatments for "off" episodes include entacapone, rasagiline, pramipexole, ropinirole, tolcapone, cabergoline, selegiline, Kynmobi (apomorphine hydrochloride sublingual film), Ongentys (opicapone capsules), or Xadago (safinamide tablets).

iv. The medication is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of apomorphine subcutaneous is not recommended in the following situations:

54. Concurrent Use with a Serotonin 5-HT_3 Antagonist. Administration of apomorphine subcutaneous in conjunction with a serotonin 5-HT_3 antagonist (e.g., ondansetron, granisetron, dolasetron, palonosetron, alosetron) can result in extreme lowering of blood pressure and loss of consciousness and is considered an absolute contraindication.[1]

55. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

115. Apokyn® subcutaneous injection [prescribing information] Louisville, KY: US WorldMeds; June 2022.
116. Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord*. 2018;33(8):1248-1266.

PRIOR AUTHORIZATION POLICY

POLICY: Phenylketonuria – Palynziq Prior Authorization Policy

- Palynziq® (pegvaliase-pqpz subcutaneous injection – BioMarin)

REVIEW DATE: 08/23/2023

OVERVIEW

Palynziq, a phenylalanine-metabolizing enzyme, is indicated to reduce blood phenylalanine concentrations in adult patients with **phenylketonuria (PKU)** who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management.[1]

Treatment with Palynziq should be managed by a healthcare provider experienced in the management of PKU. Baseline blood phenylalanine concentrations should be obtained before initiating treatment.

Dose Titration

The recommended initial induction dosage for Palynziq is 2.5 mg subcutaneously (SC) for 4 weeks.[1] This dose is then titrated over a period of at least 5 weeks to a maintenance dose of 20 mg SC once daily (QD). The maintenance dose should be individualized to achieve blood phenylalanine control (blood phenylalanine concentration ≤ 600 micromol/L). Maintain the Palynziq 20 mg QD dose for at least 24 weeks. Consider increasing the Palynziq dose to 40 mg QD in a patient who has been on 20 mg QD for at least 24 weeks without achieving blood phenylalanine control. Consider increasing the Palynziq dose to a maximum of 60 mg QD in a patient who has been on 40 mg QD for at least 16 weeks without achieving blood phenylalanine control. Discontinue Palynziq in a patient who has not achieved an adequate response after continuous treatment with the maximum dose of 60 mg QD for 16 weeks. A dose titration schedule is outlined in Table 1. Therapeutic response may not be achieved until the patient is titrated to an effective maintenance dose.

Table 1. Palynziq Dose Titration.[1]

* Additional time may be required prior to each dosage escalation based on patient tolerability; QD – Once daily.

Because of the risk of anaphylaxis Palynziq is available only through a restricted Risk Evaluation and Mitigation Strategy (REMS) program. It was unclear from the Palynziq clinical trials if all patients had tried and were non-responders to sapropterin.

Guidelines

Recommendations regarding use of Palynziq are not made in guidelines from the American College of Medical Genetics and Genomics (ACMG) [2014] or European guidelines (2017).[2,3] However, a consensus statement regarding use of Palynziq in adults with PKU was published in 2019.[4] Palynziq should be considered for all adults with PKU who have the ability to give informed consent and adhere to treatment. It is noted that some patients may show a response early on, whereas other may take 1 year or more from initiation of treatment before a reduction in blood phenylalanine concentration is observed. The definition of a "clinically meaningful" efficacy benefit should be determined by the treating clinician based on individual patient goals. Primarily, the efficacy benefit should be determined by a significant reduction in blood phenylalanine concentration from baseline.

Although ACMG and European guidelines do not offer recommendations specific to Palynziq, they do provide general principles for PKU management. ACMG guidelines suggest a target blood phenylalanine level of 120 to 360 micromol/L for all patients.[2] However, European guidelines state that patients ≥ 12

years of age with blood phenylalanine concentration < 600 micromol/L do not require treatment, and the target range for patients ≥ 12 years of age receiving treatment is 120 to 600 micromol/L.[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Palynziq. Because of the specialized skills required for evaluation and diagnosis of patients treated with Palynziq as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Palynziq to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Palynziq is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Phenylketonuria.** Approve for the duration noted if the patient meets one of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on at least one existing treatment modality; AND
       F) Note: Examples of treatment modalities include restriction of dietary phenylalanine and protein intake and prior treatment with sapropterin (Kuvan, generic).
     - **iii.** The medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).
   - **B)** Patient is Currently Receiving Palynziq. Approve for 1 year if the patient meets the following (i, ii, and iii):

G) Note: A patient who has received < 1 year of therapy or who is restarting therapy with Palynziq should be considered under Initial Therapy criteria.

- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient meets one of the following (a or b):
  - **a)** Patient meets both of the following (1 and 2):
    - **(1)** Patient is continuing to titrate Palynziq to an effective maintenance dose, per the prescriber; AND
    - **(2)** If the patient is receiving a dose of Palynziq 60 mg once daily, the treatment duration at this dose has not exceeded 16 weeks; OR
  - **b)** Patient meets both of the following (1 and 2):
    - **(1)** Patient meets one of the following (a or b):
      - **(a)** Patient's blood phenylalanine concentration is ≤ 600 micromol/L; OR
      - **(b)** Patient has achieved a ≥ 20% reduction in blood phenylalanine concentration from pre-treatment baseline (i.e., blood phenylalanine concentration before starting Palynziq therapy); AND
    - **(2)** Patient is not receiving concomitant therapy with sapropterin (Kuvan, generic).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Palynziq is not recommended in the following situations:

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

45. Palynziq™ subcutaneous injection [prescribing information]. Novato, CA: BioMarin; November 2020.
46. Vockley J, Andersson HC, Antshel KM, et al; American College of Medical Genetics and Genomics Therapeutics Committee. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. *Genet Med*. 2014 Feb;16(2):188-200.
47. van Wegberg AMJ, MacDonald A, Ahring A, et al. The complete European guidelines on phenylketonuria: diagnosis and treatment. *Orphanet J Rare Dis*. 2017;12:162.
48. Longo N, Dimmock D, Levy H, et al. Evidence- and consensus-based recommendations for the use of pegvaliase in adults with phenylketonuria. *Genet Med*. 2019 Aug;21(8):1851-1867.

PRIOR AUTHORIZATION POLICY

POLICY: Phenylketonuria – Sapropterin Prior Authorization Policy
- Kuvan™ (sapropterin dihydrochloride tablets and powder for oral solution – BioMarin, generic)
- Javygtor™ (sapropterin dihydrochloride tablets and powder for oral solution – Dr. Reddy's Laboratories)

REVIEW DATE: 08/30/2023

OVERVIEW

Sapropterin (Kuvan, Javygtor, generic), a synthetic form of the cofactor for the enzyme phenylalanine hydroxylase, is indicated to reduce blood phenylalanine levels in patients one month of age and older with hyperphenylalaninemia due to tetrahydrobiopterin-responsive **phenylketonuria** (PKU).[1] The medication should be used with a phenylalanine-restricted diet. Of note, some patients do not show a biochemical response to sapropterin. Per the prescribing information, biochemical response cannot generally be predetermined by laboratory testing and should be determined through a therapeutic trial (evaluation) of sapropterin response.

Dose Titration

The initial starting dose of sapropterin is either 10 mg/kg per day or 20 mg/kg per day. If a 10 mg/kg per day starting dose is used, the dose should be increased to 20 mg/kg if the patient's blood phenylalanine does not decrease after 1 month of treatment. If blood phenylalanine does not decrease after 1 month of treatment on 20 mg/kg per day, sapropterin should be discontinued.

Guidelines/Recommendations

According to the European guidelines for PKU (2017), there is consensus in the literature that patients with blood phenylalanine concentration > 600 micromol/L should be treated.[8] There is also consensus that patients with blood phenylalanine concentration < 360 micromol/L can remain untreated, but should be monitored. Patients with blood phenylalanine concentration between 360 to 600 micromol/L should be treated until 12 years of age. Treatment for life is recommended for any patient with PKU; however, it is also noted that patients ≥ 12 years of age with blood phenylalanine concentration < 600 micromol/L do not require treatment. All adults with PKU should have lifelong systematic follow-ups in specialized metabolic centers, due to specific risks which may occur during adulthood. With regards to target phenylalanine levels, in treated PKU patients up to 12 years of age, the target levels should be 120 to 360 micromol/L; in treated PKU patients ≥ 12 years of age, the target levels should be 120 to 600 micromol/L.

The American College of Medical Genetics and Genomics (ACMG) published practice guidelines (2014) for the diagnosis and management of phenylalanine hydroxylase (PAH) deficiency.[9] The guidelines recommend initiating treatment as early as possible, preferably within the first week of life with a goal of having blood phenylalanine levels in the treatment range within the first 2 weeks. Dietary restriction of phenylalanine intake is the mainstay of therapy for PKU. Blood phenylalanine levels in all patients should be maintained in the range of 120 to 360 micromol/L. The guidelines state that approximately 25% to 50% of patients with PAH deficiency are responsive to sapropterin. A significant decline in blood phenylalanine level is expected in responders once treatment is initiated (with phenylalanine-restricted diet); however, patients in the lower end of the treatment range (≤ 180 micromol/L) rarely show a decrease in blood phenylalanine level even if they are responsive to sapropterin. In these patients, responsiveness is determined by adding phenylalanine to the diet in a stepwise method. An improvement in neuropsychiatric

symptoms or increase in phenylalanine tolerance without a decrease in blood phenylalanine levels is sufficient reasoning to continue therapy. According to the guidelines, there is strong evidence to support life-long treatment and maintenance of metabolic control in patients with PAH deficiency.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of sapropterin (Kuvan, Javygtor, generic). Because of the specialized skills required for evaluation and diagnosis of patients treated with sapropterin as well as the monitoring required for adverse events and long-term efficacy, initial approval requires sapropterin to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of sapropterin (Kuvan, Javygtor, generic) is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Phenylketonuria.** Approve for the duration noted if the patient meets the following (A or B):
   - **A)** Initial Therapy. Approve for 12 weeks if the patient meets the following (i and ii):
     - **i.** Sapropterin is prescribed in conjunction with a phenylalanine-restricted diet; AND
     - **ii.** The medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).
   - **B)** Patients is Currently Receiving Sapropterin (Kuvan, Javygtor, generic). Approve for 1 year if the patient meets the following (i and ii):

     Note: A patient who has received < 12 weeks of therapy or who is restarting therapy with sapropterin should be considered under Initial Therapy.
     - **i.** Patient meets one of the following (a, b, or c):
       - **a)** Patient has had a clinical response (e.g., cognitive and/or behavioral improvements) as determined by the prescriber; OR
       - **b)** Patient has achieved a ≥ 20% reduction in blood phenylalanine concentration from pre-treatment baseline (i.e., blood phenylalanine concentration before starting sapropterin therapy); OR
       - **c)** Treatment with sapropterin has resulted in an increase in dietary phenylalanine tolerance, according to the prescriber; AND
     - **ii.** Patient is not receiving concomitant Palynziq (pegvaliase-pqpz subcutaneous injection) at a stable maintenance dose.

       Note: Concomitant use with Palynziq is permitted during Palynziq dose titration.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of sapropterin (Kuvan, Javygtor, generic) is not recommended in the following situations:

Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

49. Kuvan™ tablets and powder for oral solution [prescribing information]. Novato, CA: BioMarin; February 2021.
50. Levy H, Burton B, Cederbaum S, Scriver C. Recommendations for evaluation of responsiveness to tetrahydrobiopterin (BH4) in phenylketonuria and its use in treatment. *Mol Genet Metab*. 2007;92:287-291.
51. Blau N, van Spronsen FJ, Levy HL. Phenylketonuria. *Lancet*. 2010;376:1417-1427.
52. Feillet F, van Spronsen FJ, MacDonald A, et al. Challenges and pitfalls in the management of phenylketonuria. *Pediatrics*. 2010;126(2):333-341.
53. Levy HL, Milanowski A, Chakrapani A, et al for the Sapropterin Research Group. Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomized placebo-controlled study. *Lancet*. 2007;370:504-510.
54. Burton BK, Bausell H, Katz R, et al. Sapropterin therapy increases stability of blood phenylalanine levels in patients with BH4-responsive phenylketonuria (PKU). *Mol Genet Metab*. 2010;101(2-3):110-114.
55. Burton BK, Nowacka M, Hennermann JB, et al. Safety of extended treatment with sapropterin dihydrochloride in patients with phenylketonuria: results of a phase 3b study. *Mol Genet Metab*. 2011;103(4):315-322.
56. van Wegberg AMJ, MacDonald A, Ahring A, et al. The complete European guidelines on phenylketonuria: diagnosis and treatment. *Orphanet J Rare Dis*. 2017;12:162.
57. Vockley J, Andersson HC, Antshel KM, et al. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. Available at: https://www.acmg.net/docs/Phenylalanine_Hydrosylase_Deficiency_Practice_Guideline_AOP_Jan_2013.pdf. Accessed on August 18, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Pheochromocytoma – Metyrosine and Phenoxybenzamine (Oral) Prior Authorization Policy
- Demser® (metyrosine capsules – Bausch Health, generic)
- Dibenzyline® (phenoxybenzamine capsules – Concordia, generic)

REVIEW DATE: 09/20/2023

OVERVIEW

Metyrosine, a tyrosine hydroxylate inhibitor, is indicated for the treatment of patients with **pheochromocytoma** for the following uses:[1]
- Preoperative preparation of patients for surgery.
- Management of patients when surgery is contraindicated.
- Chronic treatment of patients with malignant pheochromocytoma.

Phenoxybenzamine, a long-acting, adrenergic, alpha-receptor blocking agent, is indicated for the treatment of **pheochromocytoma** to control episodes of hypertension and sweating. If tachycardia is excessive, it may be necessary to use a beta-blocking agent concomitantly.[2]

Guidelines

A clinical practice guideline was published in 2014 from the Endocrine Society regarding pheochromocytoma and paraganglioma.[3] The guidelines recommend a preoperative alpha$_1$-adrenergic receptor blocker as the first choice to control blood pressure and prevent a hypertensive crisis. Both selective and non-selective alpha-blockers have been used (e.g., phenoxybenzamine, doxazosin, prazosin, and terazosin). Calcium channel blockers are the most often used add-on drug class to further improve blood pressure control in patients already treated with alpha-adrenergic receptor blockers. Preoperative co-administration of a beta-adrenergic receptor blocker (e.g., atenolol, metoprolol, and propranolol) is utilized to control tachycardia after administration of an alpha-adrenergic receptor blocker. Metyrosine may be used in combination with an alpha-adrenergic receptor blocker for a short period before surgery to further stabilize blood pressure to reduce blood loss and volume depletion during surgery.

The National Comprehensive Cancer Network guidelines for neuroendocrine and adrenal tumors (version 1.2023 – August 02, 2023) address pheochromocytoma and paragangliomas.[4] Alpha blockade (e.g., terazosin, doxazosin, and prazosin) is recommended first-line for all hormone-secreting pheochromocytomas and paragangliomas. After alpha blockade, if additional blood pressure support is required, the additional of dihydropyridine calcium channel blockers can be considered. Metyrosine can be used in addition to alpha blockade to stabilize blood pressure.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of metyrosine and phenoxybenzamine. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with metyrosine and phenoxybenzamine as well as the monitoring required for adverse events and long-term efficacy, approval requires metyrosine and phenoxybenzamine to be prescribed by or

in consultation with a physician who specializes in the condition being treated.

Automation: None.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, and prescription receipts.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of phenoxybenzamine is recommended in those who meet the following criteria:

FDA-Approved Indication

1. Pheochromocytoma. Approve for 1 year if the patient meets the following (A and B):
- **A)** If brand Dibenzyline is requested, patient meets both of the following (i and ii):
  - **i.** Patient has tried generic phenoxybenzamine; AND
  - **ii.** Patient cannot continue to use generic phenoxybenzamine due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product which, according to the prescriber, would result in a significant allergy or a serious adverse reaction **[documentation required]**; AND
- **B)** The medication is prescribed by or in consultation with an endocrinologist or a physician who specializes in the management of pheochromocytoma.

II. Coverage of metyrosine is recommended in those who meet the following criteria:

FDA-Approved Indication

1. Pheochromocytoma. Approve for the duration noted if the patient meets ONE of the following (A or B):
- **A)** Initial Therapy. Approve for 1 year if the patient meets all of the following (i, ii, and iii):
  - **i.** Patient has tried a selective alpha blocker (e.g., doxazosin, terazosin, or prazosin); AND
  - **ii.** Patient has tried phenoxybenzamine (brand or generic); AND
  - **iii.** The medication is prescribed by, or in consultation with, an endocrinologist or a physician who specializes in the management of pheochromocytoma.
- **B)** Patient is Currently Receiving Metyrosine. Approve for 1 year if prescribed by or in consultation with an endocrinologist or a physician who specializes in the management of pheochromocytoma.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of metyrosine and phenoxybenzamine is not recommended in the following situations:

56. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

53. Demser® capsules [prescribing information]. Bridgewater, NJ: Bausch Health; July 2021.
54. Dibenzyline® capsules [prescribing information]. St. Michael, Barbados: Concordia; August 2021.
55. Lenders JWM, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2014;99(6):1915-1942.
56. The NCCN Neuroendocrine and Adrenal Tumors Clinical Practice Guidelines in Oncology (version 1.2023 – August 02, 2023) © 2023 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org/. Accessed on September 18, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Pompe Disease – Enzyme Replacement Therapy – Lumizyme Prior Authorization Policy
- Lumizyme® (alglucosidase intravenous infusion – Genzyme)

REVIEW DATE: 04/12/2023

OVERVIEW

Lumizyme, a human hydrolytic lysosomal glycogen-specific enzyme (acid α-glucosidase), is indicated for patients with **Pompe disease** (acid α-glucosidase deficiency).[1] It is produced in a Chinese hamster ovary cell line via recombinant DNA technology. After administration of Lumizyme, it is internalized into cells and transported to lysosomes where it catalyzes the breakdown of glycogen to glucose.

Disease Overview

Pompe disease (glycogen storage disease type II, or acid maltase deficiency), is a rare lysosomal storage disorder characterized by a deficiency in acid α-glucosidase activity leading to the accumulation of glycogen, particularly in muscle.[2,3] The onset, progression and severity of Pompe disease is variable. Infantile-onset Pompe disease usually manifests in the first few months of life and death often occurs in the first year of life, if left untreated.[2] Clinical manifestations of infantile-onset Pompe disease includes hypotonia, difficulty feeding, and cardiopulmonary failure.[4] Late-onset Pompe disease has more variable clinical course, can manifest any time after 12 months of age, and patients typically present with progressive muscle weakness which can progress to respiratory insufficiency.[3,4] The diagnosis of Pompe disease is established by demonstrating decreased acid α-glucosidase activity in blood, fibroblasts, or muscle tissue; or by genetic testing.[3,4] Definitive treatment of Pompe disease consists of enzyme replacement therapy with Lumizyme.[2-4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lumizyme. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lumizyme as well as the monitoring required for adverse events and long-term efficacy, approval requires Lumizyme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lumizyme is recommended in those who meet the following criteria:

FDA-Approved Indication

21. Acid Alpha-Glucosidase Deficiency (Pompe Disease). Approve for 1 year if the patient meets the following criteria (A and B):

- **A)** The diagnosis is established by one of the following (i or ii):
  - **i.** Patient has a laboratory test demonstrating deficient acid alpha-glucosidase activity in blood, fibroblasts, or muscle tissue; OR
  - **ii.** Patient has a molecular genetic test demonstrating acid alpha-glucosidase gene mutation; AND
- **B)** Lumizyme is prescribed by or in consultation with a geneticist, neurologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lumizyme is not recommended in the following situations:

57. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

117. Lumizyme® intravenous infusion [prescribing information]. Cambridge, MA: Genzyme; July 2021.
118. Chien YH, Hwu WL, Lee NC. Pompe disease: Early diagnosis and early treatment make a difference. *Pediatr Neonatol*. 2013;54:219-227.
119. Llerena Junior JC, Nascimento OJM, Oliveira ASB, et al. Guidelines for the diagnosis, treatment and clinical monitoring of patients with juvenile and adult Pompe disease. *Arq Neuropsiquiatr*. 2016;74:166-176.
120. Cupler EJ, Berger KI, Leshner RT, et al. Consensus treatment recommendations for late-onset Pompe disease. *Muscle Nerve*. 2012;45:319-333.

PRIOR AUTHORIZATION POLICY

POLICY: Pompe Disease – Enzyme Replacement Therapy – Nexviazyme Prior Authorization Policy
- Nexviazyme® (avalglucosidase alfa-ngpt intravenous infusion – Genzyme)

REVIEW DATE: 08/23/2023

OVERVIEW

Nexviazyme, a hydrolytic lysosomal glycogen-specific recombinant human α-glucosidase enzyme, is indicated for **late-onset Pompe disease** (lysosomal acid α-glucosidase deficiency) in patients ≥ 1 year of age.[1]

Disease Overview

Pompe disease (glycogen storage disease type II, or acid maltase deficiency), is a rare lysosomal storage disorder characterized by a deficiency in acid α-glucosidase activity leading to the accumulation of glycogen, particularly in muscle.[2,3] The onset, progression and severity of Pompe disease is variable. Infantile-onset Pompe disease usually manifests in the first few months of life and death often occurs in the first year of life, if left untreated.[2] Clinical manifestations of infantile-onset Pompe disease includes hypotonia, difficulty feeding, and cardiopulmonary failure.[4] Late-onset Pompe disease has a more variable clinical course and can manifest any time after 12 months of age.[3,4] Patients typically present with progressive muscle weakness which can progress to respiratory insufficiency. The diagnosis of Pompe disease is established by demonstrating decreased acid α-glucosidase activity in blood, fibroblasts, or muscle tissue, or by genetic testing.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Nexviazyme. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nexviazyme as well as the monitoring required for adverse events and long-term efficacy, approval requires Nexviazyme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nexviazyme is recommended in those who meet the following criteria:

FDA-Approved Indication

22. Acid Alpha-Glucosidase Deficiency (Pompe Disease). Approve for 1 year if the patient meets the following (A, B, C, and D):
- **A)** Patient is ≥ 1 year of age; AND
- **B)** Patient has late-onset acid alpha-glucosidase deficiency (late-onset Pompe disease); AND
- **C)** The diagnosis is established by one of the following (i or ii):
  - **i.** Patient has a laboratory test demonstrating deficient acid alpha-glucosidase activity in blood, fibroblasts, or muscle tissue; OR
  - **ii.** Patient has a molecular genetic test demonstrating acid alpha-glucosidase gene mutation; AND

D) The medication is prescribed by or in consultation with a geneticist, neurologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nexviazyme is not recommended in the following situations:

58. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

121. Nexviazyme ® intravenous infusion [prescribing information]. Cambridge, MA: Genzyme; April 2023.
122. Chien YH, Hwu WL, Lee NC. Pompe disease: Early diagnosis and early treatment make a difference. *Pediatr Neonatol*. 2013;54:219-227.
123. Llerena Junior JC, Nascimento OJM, Oliveira ASB, et al. Guidelines for the diagnosis, treatment and clinical monitoring of patients with juvenile and adult Pompe disease. *Arq Neuropsiquiatr*. 2016;74:166-176.
124. Cupler EJ, Berger KI, Leshner RT, et al. Consensus treatment recommendations for late-onset Pompe disease. *Muscle Nerve*. 2012;45:319-333.

PRIOR AUTHORIZATION POLICY

POLICY: Pompe Disease – Enzyme Replacement Therapy – Pombiliti Prior Authorization Policy
- Pombiliti® (cipaglucosidase alfa-atga intravenous infusion – Amicus)

REVIEW DATE: 10/04/2023

OVERVIEW

Pombiliti, a hydrolytic lysosomal glycogen-specific recombinant human α-glucosidase enzyme, is indicated in combination with Opfolda® (miglustat capsules), an enzyme stabilizer, for **late-onset Pompe disease** (lysosomal acid α-glucosidase deficiency) in adults weighing ≥ 40 kg who are not improving on their current enzyme replacement therapy.[1]

Disease Overview

Pompe disease (glycogen storage disease type II, or acid maltase deficiency), is a rare lysosomal storage disorder characterized by a deficiency in acid α-glucosidase activity leading to the accumulation of glycogen, particularly in muscle.[2,3] The onset, progression, and severity of Pompe disease is variable. Infantile-onset Pompe disease usually manifests in the first few months of life and death often occurs in the first year of life, if left untreated.[2] Clinical manifestations of infantile-onset Pompe disease includes hypotonia, difficulty feeding, and cardiopulmonary failure.[4] Late-onset Pompe disease has a more variable clinical course and can manifest any time after 12 months of age.[3,4] Patients typically present with progressive muscle weakness which can progress to respiratory insufficiency. The diagnosis of Pompe disease is established by demonstrating decreased acid α-glucosidase activity in blood, fibroblasts, or muscle tissue, or by genetic testing.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Pombiliti. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Pombiliti as well as the monitoring required for adverse events and long-term efficacy, approval requires Pombiliti to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Pombiliti is recommended in those who meet the following criteria:

FDA-Approved Indication

23. Acid Alpha-Glucosidase Deficiency (Pompe Disease). Approve for 1 year if the patient meets the following (A, B, C, D, E, and F):
- **A)** Patient is ≥ 18 year of age; AND
- **B)** Patient weighs ≥ 40 kg; AND
- **C)** The medication will be used in combination with Opfolda; AND
- **D)** Patient has not demonstrated an improvement in objective measures after receiving one of the following for at least one year (i or ii):

Note: Examples of objective measures include forced vital capacity (FVC) and six-minute walk test (6MWT).

i. Lumizyme (alglucosidase alfa) intravenous infusion; OR

ii. Nexviazyme (avalglucosidase alfa-ngpt) intravenous infusion; AND

E) Patient has late-onset acid alpha-glucosidase deficiency (late-onset Pompe disease) with diagnosis established by one of the following (i or ii):

i. Patient has a laboratory test demonstrating deficient acid alpha-glucosidase activity in blood, fibroblasts, or muscle tissue; OR

ii. Patient has a molecular genetic test demonstrating acid alpha-glucosidase gene mutation; AND

F) The medication is prescribed by or in consultation with a geneticist, neurologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Pombiliti is not recommended in the following situations:

59. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

125. Pombiliti ® intravenous infusion [prescribing information]. Philadelphia, PA: Amicus; September 2023.
126. Chien YH, Hwu WL, Lee NC. Pompe disease: Early diagnosis and early treatment make a difference. *Pediatr Neonatol*. 2013;54:219-227.
127. Llerena Junior JC, Nascimento OJM, Oliveira ASB, et al. Guidelines for the diagnosis, treatment and clinical monitoring of patients with juvenile and adult Pompe disease. *Arq Neuropsiquiatr*. 2016;74:166-176.
128. Cupler EJ, Berger KI, Leshner RT, et al. Consensus treatment recommendations for late-onset Pompe disease. *Muscle Nerve*. 2012;45:319-333.

PRIOR AUTHORIZATION POLICY

POLICY: Pompe Disease – Enzyme Stabilization Therapy – Opfolda Prior Authorization Policy
- Opfolda® (miglustat capsules – Amicus)

REVIEW DATE: 10/04/2023

OVERVIEW

Opfolda, an enzyme stabilizer, is indicated in combination with Pombiliti® (cipaglucosidase alfa intravenous infusion), a hydrolytic lysosomal glycogen-specific recombinant human α-glucosidase enzyme, for **late-onset Pompe disease** (lysosomal acid α-glucosidase deficiency) in adults weighing ≥ 40 kg who are not improving on their current enzyme replacement therapy.[1] Opfolda binds with, stabilizes, and reduces inactivation of Pombiliti after infusion. Bound Opfolda dissociates from Pombiliti after it is internalized and transported into lysosomes. Opfolda as monotherapy has no pharmacological activity in Pompe disease.

Disease Overview

Pompe disease (glycogen storage disease type II, or acid maltase deficiency), is a rare lysosomal storage disorder characterized by a deficiency in acid α-glucosidase activity leading to the accumulation of glycogen, particularly in muscle.[2,3] The onset, progression, and severity of Pompe disease is variable. Infantile-onset Pompe disease usually manifests in the first few months of life and death often occurs in the first year of life, if left untreated.[2] Clinical manifestations of infantile-onset Pompe disease includes hypotonia, difficulty feeding, and cardiopulmonary failure.[4] Late-onset Pompe disease has a more variable clinical course and can manifest any time after 12 months of age.[3,4] Patients typically present with progressive muscle weakness which can progress to respiratory insufficiency. The diagnosis of Pompe disease is established by demonstrating decreased acid α-glucosidase activity in blood, fibroblasts, or muscle tissue, or by genetic testing.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Opfolda. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Opfolda as well as the monitoring required for adverse events and long-term efficacy, approval requires Opfolda to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Opfolda is recommended in those who meet the following criteria:

FDA-Approved Indication

24. Acid Alpha-Glucosidase Deficiency (Pompe Disease). Approve for 1 year if the patient meets the following (A, B, C, D, E, and F):
- **A)** Patient is ≥ 18 year of age; AND
- **B)** Patient weighs ≥ 40 kg; AND

C) The medication will be used in combination with Pombiliti; AND

D) Patient has not demonstrated an improvement in objective measures after receiving one of the following for at least one year (i or ii):
Note: Examples of objective measures include forced vital capacity (FVC) and six-minute walk test (6MWT)
- **i.** Lumizyme (alglucosidase alfa) intravenous infusion; OR
- **ii.** Nexviazyme (avalglucosidase alfa-ngpt) intravenous infusion; AND

E) Patient has late-onset acid alpha-glucosidase deficiency (late-onset Pompe disease) with diagnosis established by one of the following (i or ii):
- **i.** Patient has a laboratory test demonstrating deficient acid alpha-glucosidase activity in blood, fibroblasts, or muscle tissue; OR
- **ii.** Patient has a molecular genetic test demonstrating acid alpha-glucosidase gene mutation; AND

F) The medication is prescribed by or in consultation with a geneticist, neurologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Opfolda is not recommended in the following situations:

60. Gaucher Disease. An alternate dosage of miglustat is available for the treatment of Gaucher disease.[5]

61. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Proprotein Convertase Subtilisin Kexin Type 9 Inhibitors – Praluent Prior Authorization Policy
- Praluent® (alirocumab subcutaneous injection – Regeneron)

REVIEW DATE: 04/26/2023

OVERVIEW

Praluent, a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor antibody, is indicated for the following uses:[1]

- **Established cardiovascular (CV) disease**, in adults to reduce the risk of myocardial infarction (MI), stroke, and unstable angina requiring hospitalization.
- **Primary hyperlipidemia** (including **heterozygous familial hypercholesterolemia [HeFH]**), in adults as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe) to reduce low-density lipoprotein cholesterol (LDL-C).
- **Homozygous familial hypercholesterolemia (HoFH)**, in adults as an adjunct to other LDL-C lowering therapies, to reduce LDL-C.

The safety and efficacy of Praluent in children have not been established.[1] Repatha® (evolocumab subcutaneous injection) is another PCSK9 inhibitor.[2] Leqvio® (inclisiran subcutaneous injection), a small interfering ribonucleic acid (RNA) directed to PCSK9 messenger RNA, is a similar product.[3]

Guidelines

Many guidelines are available regarding the treatment of patients with dyslipidemia.[4-10] For patients with elevated LDL-C, statins are the cornerstone of therapy and recommended first-line to be used at maximally tolerated doses due to the established benefits regarding the reduction of CV risks. Atorvastatin 40 mg to 80 mg once daily (QD) and rosuvastatin 20 mg to 40 mg QD are considered high-intensity statins as they achieve LDL-C lowering of ≥ 50%. Ezetimibe is usually the next therapy added.

- The **American College of Cardiology Expert Consensus Decision Pathway on the Role of Non-Statin Therapies** for LDL-Cholesterol Lowering in the Management of Atherosclerotic cardiovascular disease (ASCVD) Risk (2022) make several recommendations regarding PCSK9 inhibitors.[4] For adults with clinical ASCVD at very high risk (e.g., patients with major ASCVD events, HeFH, diabetes) who are on statin therapy for secondary prevention, the general goal is ≥ 50% LDL-C reduction and an LDL-C < 55 mg/dL with maximally tolerated statin therapy. If the above goals are not achieved, the initial non-statin agents recommended include ezetimibe and/or a PCSK9 monoclonal antibody (i.e., Repatha or Praluent). For adults without clinical ASCVD or diabetes or LDL-C ≥ 190 mg/dL who have undergone subclinical atherosclerosis imaging, if the coronary artery calcium score is ≥ 1,000 Agatston units, PCSK9 monoclonal antibodies (i.e., Repatha or Praluent) may be non-statin agents to consider following high-intensity statin therapy and ezetimibe to achieve the goal of a ≥ 50% LDL-C reduction (and LDL-C threshold < 70 mg/dL).
- The **American Heart Association/American College of Cardiology guidelines on the management of blood cholesterol** (updated 2018) defines ASCVD as an acute coronary syndrome, those with a history of MI, stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack, or peripheral arterial disease.[5,6] Although LDL-C thresholds are not always recognized, in general, an LDL-C < 70 mg/dL is recommended for most patients with ASCVD to reduce CV risk. Use of a PCSK9 as an adjunct is justified if this goal is not met with maximally tolerated statins.[5,6] Additionally, guidelines and reviews have recognized that patients with an elevated coronary

artery calcium or calcification score (e.g., ≥ 300 Agatston units) are at an increased risk of CV events.[8,11-14]

- The **National Lipid Association** published guidelines for the screening, diagnosis, and management of pediatric and adult patients with familial hypercholesterolemia (2011).[9] Genetic testing can identify HoFH and HeFH in some cases. Also, HeFH can be diagnosed utilizing Simon Broome criteria or Dutch Lipid Clinical Network criteria. Patients with an untreated LDL-C ≥ 190 mg/dL suggest familial hypercholesterolemia. Statins are the initial treatment for all adults with familial hypercholesterolemia, usually at high-potency doses. Ezetimibe can also be added. In general, for patients with HeFH who have not yet manifested ASCVD, LDL-C levels ≤ 100 mg/dL are recommended.
- The **2014 HoFH position paper from the Consensus Panel on familial hypercholesterolemia of the European Atherosclerosis Society** states the diagnosis of HoFH is made based on genetic or clinical criteria.[15] A definitive diagnosis can be made by genetic confirmation of two mutant alleles at the low density lipoprotein receptor, apolipoprotein B, PCSK9, or low-density lipoprotein receptor adaptor protein 1 gene locus. However, in some patients genetic confirmation remains elusive. Historically, HoFH has been commonly diagnosed based on LDL-C levels such as an untreated LDL-C > 500 mg/dL, or a treated LDL-C ≥ 300 mg/dL. Also confirming the diagnosis is the presence of xanthomas (cutaneous or tendinous) before the age of 10 years or a family history of elevated LDL-C levels consistent with HeFH in both parents. Other clinical manifestations of HoFH include arcus cornea or xanthelasma. Initial therapy for HoFH is high-intensity statins.[15] Other guidelines note that ezetimibe and PCSK9 inhibitors can be added for patients with HoFH if further reductions are needed; Juxtapid® (lomitapide capsules) and Evkeeza® (evinacumab-dgnb intravenous infusion) can be considered.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Praluent. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and monitoring, approval requires Praluent to be prescribed by or in consultation with a physician who specializes in the condition being treated. A patient who has previously met initial therapy criteria for Praluent for the requested indication under the Coverage Review Department and is currently receiving the requested therapy is only required to meet continuation of therapy criteria (i.e., currently receiving therapy). If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Praluent, or is restarting Praluent, initial criteria must be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Praluent is recommended in those who meet the following criteria:

FDA-Approved Indications

35. Atherosclerotic Cardiovascular Disease.* Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets all of the following (i, ii, iii, and iv):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has had one of the following conditions or diagnoses (a, b, c, d, or e):
  - **a)** A previous myocardial infarction or a history of an acute coronary syndrome; OR
  - **b)** Angina (stable or unstable); OR
  - **c)** A past of stroke or transient ischemic attack; OR
  - **d)** Peripheral arterial disease; OR

e) Patient has undergone a coronary or other arterial revascularization procedure in the past; AND

H) Note: Examples include coronary artery bypass graft surgery, percutaneous coronary intervention, angioplasty, and coronary stent procedures.

iii. Patient meets one of the following (a or b):

a) Patient meets both of the following [(1) and (2)]:

(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND

(2) Low-density lipoprotein cholesterol level after this treatment remains ≥ 70 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting one of the following [(1) or (2)]:

(1) Patient experienced statin-related rhabdomyolysis; OR

I) Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]).

(2) Patient meets all of the following [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND

J) Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

K) (b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND

L) (c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND

M) Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

iv. Medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders; OR

B) Patient Currently Receiving Praluent. Approve if according to the prescribing physician, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Praluent for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Praluent, Initial Therapy criteria must be met.

36. Heterozygous Familial Hypercholesterolemia (HeFH).* Approve for 1 year if the patient meets ONE the following (A or B):

A) Initial Therapy. Approve if the patient meets all of the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets one of the following (a, b, or c):

a) Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents); OR

b) Patient has genetic confirmation of heterozygous familial hypercholesterolemia by mutations in the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9, or low-density lipoprotein receptor adaptor protein 1 gene; OR

c) Patient has been diagnosed with heterozygous familial hypercholesterolemia meeting one of the following diagnostic criteria thresholds [(1) or (2)]:

(1) Prescribing physician confirms that the Dutch Lipid Network criteria score was > 5; OR

(2) Prescribing physician confirms that Simone Broome criteria met the threshold for "definite" or "possible (or probable)" familial hypercholesterolemia; AND

iii. Patient meets one of the following (a or b):

(1) Patient meets both of the following [(1) and (2)]:

1. Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND

2. Low-density lipoprotein cholesterol level after this treatment remains ≥ 70 mg/dL; OR

(2) Patient has been determined to be statin intolerant by meeting one of the following [(1) or (2)]:

1. Patient experienced statin-related rhabdomyolysis; OR

N) Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]).

2. Patient meets all of the following [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND

O) Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

P) **(b)** The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND

Q) **(c)** When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND

R) Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

iv. Medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders; OR

B) Patient Currently Receiving Praluent. Approve if according to the prescribing physician, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Praluent for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Praluent, Initial Therapy criteria must be met.

37. Homozygous Familial Hypercholesterolemia (HoFH).* Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets all of the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets one of the following (a, b, or c):

a) Patient has genetic confirmation of two mutant alleles at the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 gene locus; OR

b) Patient has an untreated low-density lipoprotein (LDL-C) level > 500 mg/dL AND meets one of the following [(1) or (2)]:

Note: Untreated refers to prior therapy with any antihyperlipidemic agent.

(1) Patient had clinical manifestations of homozygous familial hypercholesterolemia before 10 years of age; OR

S) Note: Clinical manifestations of homozygous familial hypercholesterolemia are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas, or xanthelasma.

(2) Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia; OR

T) Note: An example of heterozygous familial hypercholesterolemia in both parents would be if both had an untreated LDL-C level ≥ 190 mg/dL and/or an untreated total cholesterol level > 250 mg/dL.

c) Patient has a treated LDL-C level ≥ 300 mg/dL AND meets one of the following [(1) or (2)]:

Note: Treated refers to after therapy with at least one antihyperlipidemic agent. Some examples of antihyperlipidemic agents include statins (e.g., atorvastatin, rosuvastatin, lovastatin, simvastatin, pravastatin), ezetimibe, a PCSK9 inhibitor (e.g., Repatha [evolocumab subcutaneous injection]), Evkeeza (evinacumab-dgnb intravenous infusion), and Juxtapid (lomitapide capsules).

1. Patient had clinical manifestations of homozygous familial hypercholesterolemia before 10 years of age; OR

Note: Examples of clinical manifestations of homozygous familial hypercholesterolemia are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma.

2. Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia; AND

U) Note: An example of heterozygous familial hypercholesterolemia in both parents would be if both had an untreated LDL-C ≥ 190 mg/dL and/or an untreated total cholesterol > 250 mg/dL.

iii. Patient meets one of the following (a or b):

a) Patient meets both of the following [(1) and (2)]:

(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND

(2) LDL-C level after this treatment remains ≥ 70 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting one of the following criteria [(1) or (2)]:

(1) Patient experienced statin-related rhabdomyolysis; OR

Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR

(2) Patient meets all of the following [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND

V) Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

W) (b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND

X) (c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND

Y) Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

iv. Medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders; OR

B) Patient Currently Receiving Praluent. Approve if according to the prescribing physician, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Praluent for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Praluent, Initial Therapy criteria must be met.

38. Primary Hyperlipidemia.* Approve for 1 year if the patient meets ONE of the following (A or B):

Note: This is not associated with atherosclerotic cardiovascular disease (ASCVD) or heterozygous familial hypercholesterolemia (HeFH) and may be referred to as combined hyperlipidemia, hypercholesterolemia (pure, primary), dyslipidemia, or increased/elevated low-density lipoprotein cholesterol (LDL-C) levels.

A) Initial Therapy. Approve if the patient meets all of the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Patient has a coronary artery calcium or calcification score ≥ 300 Agatston units; AND

iii. Patient meets one of the following (a or b):

a) Patient meets all of the following [(1), (2), and (3)]:

(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]); AND

(2) Patient has tried the one high-intensity statin therapy above along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND

(3) LDL-C level after this treatment regimen remains ≥ 100 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting one of the following [(1) or (2)]:

(1) Patient experienced statin-related rhabdomyolysis; OR

Z) Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]).

(2) Patient meets all of the following [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND

AA) Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).
BB) (b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND
CC) (c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND
Note: Examples of skeletal-related muscle symptoms include myopathy or myalgia.

iv. Medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders; OR

B) Patient Currently Receiving Praluent. According to the prescribing physician, the patient has experienced a response to therapy.
Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Praluent for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Praluent, Initial Therapy criteria must be met.

Note:
* A patient may have diagnoses that pertain to more than one FDA-approved indication, therefore, consider review under different approval conditions, if applicable (e.g., a patient with heterozygous familial hypercholesterolemia or homozygous familial hypercholesterolemia may have had a clinical ASCVD event, a patient with primary hyperlipidemia may have heterozygous familial hypercholesterolemia).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Praluent is not recommended in the following situations:

53. Concurrent use of Praluent with Repatha (evolocumab subcutaneous injection) or Leqvio (inclisiran subcutaneous injection). Repatha is another PCSK9 inhibitor and should not be used with Praluent.[2] Leqvio, a small interfering ribonucleic acid (RNA) directed to PCSK9 messenger RNA, is a similar product and should not be given with Praluent.[3]

54. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX A.

Simon Broome Register Diagnostic Criteria.[16]
LDL-C – Low-density lipoprotein cholesterol; LDL – Low-density lipoprotein; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

APPENDIX B.

Dutch Lipid Network Criteria.[17]

LDL-C – Low-density lipoprotein cholesterol; CAD – Coronary artery disease; LDLR – Low-density lipoprotein receptor; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

PRIOR AUTHORIZATION POLICY

POLICY: Proprotein Convertase Subtilisin Kexin Type 9 Inhibitors – Repatha Prior Authorization Policy
- Repatha® (evolocumab subcutaneous injection [single-use prefilled syringes and Pushtronex™ system] – Amgen)

REVIEW DATE: 04/26/2023

OVERVIEW

Repatha, a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor antibody, is indicated for the following uses:[1]

- **Established cardiovascular (CV) disease**, in adults to reduce the risk of myocardial infarction (MI), stroke, and coronary revascularization.
- **Primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH])**, in adults as an adjunct to diet, alone or in combination with other low-density lipoprotein cholesterol (LDL-C)-lowering therapies to reduce LDL-C.
- **HeFH, in pediatric patients ≥ 10 years of age**, as an adjunct to diet and other LDL-C lowering therapies.
- **Homozygous familial hypercholesterolemia (HoFH)**, as an adjunct to diet and other low-density lipoprotein (LDL)-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients ≥ 10 years of age and older, to reduce LDL-C.

The safety and effectiveness of Repatha have not been established in pediatric patients with HeFH or HoFH who are younger than 10 years of age.[1] Another PCSK9 inhibitor that is available is Praluent® (alirocumab subcutaneous injection).[2] Leqvio® (inclisiran subcutaneous injection), a small interfering ribonucleic acid (RNA) directed to PCSK9 messenger RNA, is a similar product.[3]

Guidelines

Many guidelines are available regarding the treatment of patients with dyslipidemia.[4-10] For patients with elevated LDL-C, statins are the cornerstone of therapy and recommended first-line to be used at maximally tolerated doses due to the established benefits regarding the reduction of CV risks. Atorvastatin 40 mg to 80 mg once daily (QD) and rosuvastatin 20 mg to 40 mg QD are considered high-intensity statins as they achieve LDL-C lowering of ≥ 50%. Ezetimibe is usually the next therapy added.

- The **American College of Cardiology Expert Consensus Decision Pathway on the Role of Non-Statin Therapies** for LDL-Cholesterol Lowering in the Management of Atherosclerotic cardiovascular disease (ASCVD) Risk (2022) make several recommendations regarding PCSK9 inhibitors.[4] For adults with clinical ASCVD at very high risk (e.g., patients with major ASCVD events, HeFH, diabetes) who are on statin therapy for secondary prevention, the general goal is ≥ 50% LDL-C reduction and an LDL-C < 55 mg/dL with maximally tolerated statin therapy. If the above goals are not achieved, the initial non-statin agents recommended include ezetimibe and/or a PCSK9 monoclonal antibody (i.e., Repatha or Praluent). For adults without clinical ASCVD or diabetes or LDL-C ≥ 190 mg/dL who have undergone subclinical atherosclerosis imaging, if the coronary artery calcium score is ≥ 1,000 Agatston units, PCSK9 monoclonal antibodies (i.e., Repatha or Praluent) may be non-statin agents to consider following high-intensity statin therapy and ezetimibe to achieve the goal of a ≥ 50% LDL-C reduction (and LDL-C threshold < 70 mg/dL).
- The **American Heart Association/American College of Cardiology guidelines on the management of blood cholesterol** (updated 2018) defines ASCVD as an acute coronary syndrome, those with a

history of MI, stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack, or peripheral arterial disease.[5,6] Although LDL-C thresholds are not always recognized, in general, an LDL-C < 70 mg/dL is recommended for most patients with ASCVD to reduce CV risk. Use of a PCSK9 as an adjunct is justified if this goal is not met with maximally tolerated statins.[5,6] Additionally, guidelines and reviews have recognized that patients with an elevated coronary artery calcium or calcification score (e.g., ≥ 300 Agatston units) are at an increased risk of CV events.[8,11-14]

- The **National Lipid Association** published guidelines for the screening, diagnosis, and management of pediatric and adult patients with familial hypercholesterolemia (2011).[9] Genetic testing can identify HoFH and HeFH in some cases. Also, HeFH can be diagnosed utilizing Simon Broome criteria or Dutch Lipid Clinical Network criteria. Patients with an untreated LDL-C ≥ 190 mg/dL suggest familial hypercholesterolemia. Statins are the initial treatment for all adults with familial hypercholesterolemia, usually at high-potency doses. Ezetimibe can also be added. In general, for patients with HeFH who have not yet manifested ASCVD, LDL-C levels ≤ 100 mg/dL are recommended.
- The **2014 HoFH position paper from the Consensus Panel on familial hypercholesterolemia of the European Atherosclerosis Society** states the diagnosis of HoFH is made based on genetic or clinical criteria.[15] A definitive diagnosis can be made by genetic confirmation of two mutant alleles at the LDL receptor, apolipoprotein B, PCSK9, or LDL receptor adaptor protein 1 gene locus. However, in some patients genetic confirmation remains elusive. Historically, HoFH has been commonly diagnosed based on LDL-C levels such as an untreated LDL-C > 500 mg/dL, or a treated LDL-C ≥ 300 mg/dL. Also confirming the diagnosis is the presence of xanthomas (cutaneous or tendinous) before the age of 10 years or a family history of elevated LDL-C levels consistent with HeFH in both parents. Other clinical manifestations of HoFH include arcus cornea or xanthelasma. Initial therapy for HoFH is high-intensity statins.[15] Other guidelines note that ezetimibe and PCSK9 inhibitors can be added for patients with HoFH if further reductions are needed; Juxtapid® (lomitapide capsules) and Evkeeza® (evinacumab-dgnb intravenous infusion) can be considered.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Repatha. All approvals are provided for the duration noted below. Due to the specialized skills required for evaluation and monitoring, approval requires Repatha to be prescribed by or in consultation with a physician who specializes in the condition being treated. Only a patient who has previously met initial therapy criteria for Repatha for the requested indication under the Coverage Review Department and is currently receiving the requested therapy is only required to meet continuation of therapy criteria (i.e., currently receiving therapy). If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Repatha, or is restarting Repatha, initial criteria must be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Repatha is recommended in those who meet the following criteria:

FDA-Approved Indications

39. Atherosclerotic Cardiovascular Disease.* Approve for 1 year if the patient meets one of the following (A or B):

C) Initial Therapy. Approve if the patient meets allow the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Patient has had one of the following conditions or diagnoses (a, b, c, d, or e):

a) A previous myocardial infarction or a history of an acute coronary syndrome; OR

b) Angina (stable or unstable); OR

c) A past of stroke or transient ischemic attack; OR

d) Peripheral arterial disease; OR

e) Patient has undergone a coronary or other arterial revascularization procedure in the past; AND

Note: Examples include coronary artery bypass graft surgery, percutaneous coronary intervention, angioplasty, and coronary stent procedures.

iii. Patient meets one of the following (a or b):

~~**a)**~~ Patient meets both of the following [(1) and (2)]:

(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND

(2) Low-density lipoprotein cholesterol level after this treatment remains ≥ 70 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting one of the following criteria [(1) or (2)]:

(1) Patient experienced statin-related rhabdomyolysis; OR

Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR

(2) Patient meets all of the following [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND

DD) Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

EE) (b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND

FF) (c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND

GG) Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

iv. Medication is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders; OR

D) Patient Currently Receiving Repatha. Approve if according to the prescribing physician, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Repatha for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Repatha, Initial Therapy criteria must be met.

40. Heterozygous Familial Hypercholesterolemia (HeFH).* Approve for 1 year if the patient meets ONE of the following (A or B):

C) Initial Therapy. Approve if the patient meets all of the following (i, ii, iii, and iv):

i. Patient is ≥ 10 years of age; AND

ii. Patient meets one of the following (a, b, or c):

(1) Patient has an untreated low-density lipoprotein cholesterol (LDL-C) ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents); OR

(2) Patient has genetic confirmation of heterozygous familial hypercholesterolemia by mutations in the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9, or low-density lipoprotein receptor adaptor protein 1 gene; OR

(3) Patient has been diagnosed with heterozygous familial hypercholesterolemia by meeting one of the following diagnostic criteria thresholds [(1) or (2)]:

(1) Prescribing physician confirms that the Dutch Lipid Network criteria score was > 5; OR

(2) Prescribing physician confirms that Simone Broome criteria met the threshold for "definite" or "possible (or probable)" familial hypercholesterolemia; AND

iii. Patient meets one of the following (a or b):

a) Patient meets both of the following ([(1) and (2)]:

(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND

(2) Low-density lipoprotein cholesterol (LDL-C) level after this treatment remains ≥ 70 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting one of the following [(1) or (2)]:

(1) Patient experienced statin-related rhabdomyolysis; OR

Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]).

(2) Patient meets all of the following [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND

HH) Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

II) (b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND

JJ) (c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND

KK) Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

iv. Medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders; OR

D) Patient Currently Receiving Repatha. Approve if according to the prescribing physician, the patient has experienced a response to therapy.
Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Repatha for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Repatha, Initial Therapy criteria must be met.

41. Homozygous Familial Hypercholesterolemia (HoFH).* Approve for 1 year if the patient meets one of the following (A or B):

C) Initial Therapy. Approve if the patient meets all of the following (i, ii, iii, and iv):

i. Patient is ≥ 10 years of age; AND

ii. Patient meets one of the following (a, b, or c):

a) Patient has genetic confirmation of two mutant alleles at the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 gene locus; OR

b) Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level > 500 mg/dL AND meets one of the following [(1) or (2)]:
Note: Untreated refers to therapy with any antihyperlipidemic agent.

(1) Patient had clinical manifestations of homozygous familial hypercholesterolemia before 10 years of age; OR

LL) Note: Clinical manifestations of homozygous familial hypercholesterolemia are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas, or xanthelasma.

(2) Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia; OR

MM) Note: An example of heterozygous familial hypercholesterolemia in both parents would be if both had an untreated LDL-C level ≥ 190 mg/dL and/or an untreated total cholesterol level > 250 mg/dL.

c) Patient has a treated LDL-C level ≥ 300 mg/dL AND meets one of the following [(1) or (2)]:
Note: Treated refers to after therapy with at least one antihyperlipidemic agent. Some examples of antihyperlipidemic agents include statins (e.g., atorvastatin, rosuvastatin, lovastatin, simvastatin, pravastatin), ezetimibe, a PCSK9 inhibitor (e.g., Praluent [alirocumab subcutaneous injection]), Evkeeza (evinacumab-dgnb intravenous infusion), or Juxtapid (lomitapide capsules).

(1) Patient had clinical manifestations of homozygous familial hypercholesterolemia before 10 years of age; OR
Note: Examples of clinical manifestations of homozygous familial hypercholesterolemia are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma.

(2) Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia; AND

NN) Note: An example of heterozygous familial hypercholesterolemia in both parents would be if both had an untreated LDL-C ≥ 190 mg/dL and/or an untreated total cholesterol > 250 mg/dL.

iii. Patient meets one of the following (a or b):

a) Patient meets both of the following [(1) and (2)]:

(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND

(2) LDL-C level after this treatment remains ≥ 70 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting one of the following criteria [(1) or (2)]:

(1) Patient experienced statin-related rhabdomyolysis; OR

Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR

(2) Patient meets all of the following [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND

OO) Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

PP) (b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND

QQ) (c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND

RR) Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

iv. Medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders; OR

D) Patient Currently Receiving Repatha. Approve if according to the prescribing physician, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Repatha for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Repatha, Initial Therapy criteria must be met.

42. Primary Hyperlipidemia.* Approve for 1 year if the patient meets ONE of the following (A or B):

Note: This is not associated with atherosclerotic cardiovascular disease (ASCVD), heterozygous familial hypercholesterolemia (HeFH), or homozygous familial hypercholesterolemia (HoFH) and may be referred to as combined hyperlipidemia, hypercholesterolemia (pure, primary), dyslipidemia, or increased/elevated low-density lipoprotein cholesterol (LDL-C) levels.

C) Initial Therapy. Approve if the patient meets all of the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND
ii. Patient has a coronary artery calcium or calcification score ≥ 300 Agatston units; AND
iii. Patient meets one of the following criteria (a or b):
a) Patient meets all of the following [(1), (2), and (3)]:
~~(1)~~ Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]); AND
~~(2)~~ Patient has tried one high-intensity statin therapy above along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND
~~(3)~~ LDL-C level after this treatment regimen remains ≥ 100 mg/dL; OR
b) Patient has been determined to be statin intolerant by meeting one of the following [(1) or (2)]:
(1) Patient experienced statin-related rhabdomyolysis; OR
Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR
(2) Patient meets all of the following [(a), (b), and (c)]:
(a) Patient experienced skeletal-related muscle symptoms; AND
SS) Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).
TT) (b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND
UU) (c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND
VV) Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.
iv. Medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders; OR
D) Patient Currently Receiving Repatha. Approve if according to the prescribing physician, the patient has experienced a response to therapy.
Note: Examples of a response to therapy include decreasing low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Repatha for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Repatha, Initial Therapy criteria must be met.

Note:
* A patient may have diagnoses pertain to more than one FDA-approved indication, therefore, consider review under different approval conditions, if applicable (e.g., a patient with heterozygous familial hypercholesterolemia or homozygous familial hypercholesterolemia may have had a clinical ASCVD event, a patient with primary hyperlipidemia may have heterozygous familial hypercholesterolemia).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Repatha is not recommended in the following situations:

55. Concurrent use of Repatha with Praluent (alirocumab subcutaneous injection) or Leqvio (inclisiran subcutaneous injection). Praluent is another PCSK9 inhibitor and should not be used with Repatha.[2] Leqvio, a small interfering ribonucleic acid (RNA) directed to PCSK9 messenger RNA, is a similar product and should not be given with Repatha.[3]

56. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX A

Simon Broome Register Diagnostic Criteria.[16]
LDL-C – Low-density lipoprotein cholesterol; LDL – Low-density lipoprotein; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

APPENDIX B.

Dutch Lipid Network Criteria.[17]

LDL-C – Low-density lipoprotein cholesterol; CAD – Coronary artery disease; LDLR – Low-density lipoprotein receptor; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

PRIOR AUTHORIZATION POLICY

POLICY: Proprotein Convertase Subtilisin Kexin Type 9 Related Products – Leqvio Prior Authorization Policy
- Leqvio® (inclisiran subcutaneous injection – Novartis)

REVIEW DATE: 04/26/2023; selected revision 08/30/2023

OVERVIEW

Leqvio, a small interfering ribonucleic acid (RNA) directed to proprotein convertase subtilisin kexin type 9 (PCSK9) messenger RNA, is indicated as an adjunct to diet and statin therapy for the treatment of adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce low-density lipoprotein cholesterol (LDL-C).[1] The safety and effectiveness have not been established in pediatric patients.

Dosing Information

Leqvio is given as a subcutaneous injection and should be administered by a healthcare professional. The dose is 284 mg given as a single subcutaneous injection initially, again at 3 months, and then once every 6 months.

Guidelines

Many guidelines are available regarding the treatment of patients with dyslipidemia which include the management of HeFH and atherosclerotic cardiovascular disease (ASCVD).[2-10] For patients with elevated LDL-C, statins are the cornerstone of therapy and recommended first-line to be used at maximally tolerated doses due to the established benefits regarding the reduction of cardiovascular (CV) risks. Atorvastatin 40 mg to 80 mg once daily (QD) and rosuvastatin 20 mg to 40 mg QD are considered high-intensity statins as they achieve LDL-C lowering of ≥ 50%.

- The **American College of Cardiology (ACC) Expert Consensus Decision Pathway on the Role of Non-Statin Therapies** for LDL-C Lowering in the Management of ASCVD Risk (2022) make several recommendations regarding PCSK9 inhibitors and Leqvio.[2] For adults with clinical ASCVD at very high risk (e.g., patients with major ASCVD events, HeFH, diabetes) who are on statin therapy for secondary prevention, the general goal is ≥ 50% LDL-C reduction and an LDL-C < 55 mg/dL with maximally tolerated statin therapy. If the above goals are not achieved, the initial non-statin agents recommended include ezetimibe and/or a PCSK9 monoclonal antibody (i.e., Repatha® [evolocumab subcutaneous injection] or Praluent® [alirocumab subcutaneous injection]). Leqvio may also be considered.
- **The American Heart Association (AHA)/ACC guidelines for chronic coronary disease (2023)** state that in patients with chronic coronary disease on maximally tolerated statin therapy who have an LDL-C level ≥ 70 mg/dL, and in whom ezetimibe and PCSK9 inhibitors are deemed insufficient or not tolerated, it may be reasonable to add Nexletol® (bempedoic acid tablets) or Leqvio (in place of a PCSK9 inhibitor) to further reduce LDL-C levels.[10]
- **The AHA** published a scientific statement regarding familial hypercholesterolemia (2015).[8] Key points are that the condition may start early (in childhood or adolescence) and is noted by LDL-C levels ≥ 190 mg/dL. Premature CV disease can result. Diagnosis can be confirmed by genetic testing. The Dutch Lipid Clinic Network criteria and Simon Broome criteria may also be used which incorporate cholesterol levels, family history, clinical findings, and physical manifestations. Aggressive lipid-lowering therapy is recommended to achieve LDL-C reductions of at least 50%.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Leqvio. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and monitoring, approval requires Leqvio to be prescribed by or in consultation with a physician who specializes in the condition being treated. A patient who has previously met Initial Therapy criteria for Leqvio for the requested indication under the Coverage Review Department and is currently receiving Leqvio is only required to meet continuation of therapy criteria (i.e., currently receiving therapy). If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Leqvio, or is restarting Leqvio, Initial Therapy criteria must be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Leqvio is recommended in those who meet one of the following criteria:

FDA-Approved Indications

43. Heterozygous Familial Hypercholesterolemia (HeFH).* Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets all of the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets one of the following (a, b, or c):

a) Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents); OR

b) Patient has genetic confirmation of heterozygous familial hypercholesterolemia by mutations in the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9, or low-density lipoprotein receptor adaptor protein 1 gene; OR

c) Patient has been diagnosed with heterozygous familial hypercholesterolemia meeting one of the following diagnostic criteria thresholds [(1) or (2)]:

(1) Prescribing physician confirms that the Dutch Lipid Network criteria score was > 5; OR

(2) Prescribing physician confirms that Simone Broome criteria met the threshold for "definite" or "possible (or probable)" familial hypercholesterolemia; AND

iii. Patient meets one of the following (a or b):

a) Patient meets all of the following [(1), (2), and (3)]:

(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single entity or as a combination product]); AND

(2) Patient has tried one high-intensity statin along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND

(3) LDL-C level after this treatment regimen remains ≥ 70 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting one of the following [(1) or (2)]:

1. Patient experienced statin-related rhabdomyolysis; OR
Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]).

2. Patient meets all of the following [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND

Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

(b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND

(c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND

Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

iv. Medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders; OR

E) Patient Currently Receiving Leqvio. Approve if according to the prescribing physician, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing LDL-C, total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Leqvio for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Leqvio, Initial Therapy criteria must be met.

44. Primary Hyperlipidemia.* Approve for 1 year if the patient meets ONE of the following (A or B):

Note: This is not associated with atherosclerotic cardiovascular disease (ASCVD) or heterozygous familial hypercholesterolemia (HeFH) and may be referred to as combined hyperlipidemia, hypercholesterolemia (pure, primary), dyslipidemia, or increased/elevated low-density lipoprotein cholesterol (LDL-C) levels.

A) Initial Therapy. Approve if the patient meets all of the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Patient has a coronary artery calcium or calcification score ≥ 300 Agatston units; AND

iii. Patient meets one of the following (a or b):

a) Patient meets all of the following [(1]), (2), and (3)]:

(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]); AND

(2) Patient has tried the one high-intensity statin therapy above along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND

(3) LDL-C level after this treatment regimen remains ≥ 100 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting one of the following [(1) or (2)]:

1. Patient experienced statin-related rhabdomyolysis; OR

Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]).

2. Patient meets all of the following [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND

Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

(b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND

(c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND

Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

iv. Medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders; OR

B) Patient Currently Receiving Leqvio. Approve if according to the prescribing physician, the patient has experienced a response to therapy.

Note: Examples of a response to therapy include decreasing LDL-C, total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Leqvio for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Leqvio, Initial Therapy criteria must be met.

Other Uses with Supportive Evidence

3. Atherosclerotic Cardiovascular Disease.* Approve for 1 year if the patient meets ONE of the following (A or B):

E) Initial Therapy. Approve if the patient meets all of the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Patient has had one of the following conditions or diagnoses (a, b, c, d, e, or f):

a) A previous myocardial infarction or a history of an acute coronary syndrome; OR

b) Angina (stable or unstable); OR

c) A past of stroke or transient ischemic attack; OR

d) Coronary artery disease; OR

e) Peripheral arterial disease; OR

f) Patient has undergone a coronary or other arterial revascularization procedure in the past; AND

Note: Examples include coronary artery bypass graft surgery, percutaneous coronary intervention, angioplasty, and coronary stent procedures.

iii. Patient meets one of the following (a or b):

a) Patient meets all of the following ([(1), (2), and (3)]:

(1) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single entity or as a combination product]); AND

(2) Patient has tried one high-intensity statin along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND

(3) Low-density lipoprotein cholesterol (LDL-C) level after this treatment regimen remains ≥ 70 mg/dL; OR

b) Patient has been determined to be statin intolerant by meeting one of the following [(1) or (2)]:

(1) Patient experienced statin-related rhabdomyolysis; OR

Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]).

(2) Patient meets all of the following [(a), (b), and (c)]:

(a) Patient experienced skeletal-related muscle symptoms; AND
Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

(b) The skeletal-muscle related symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or combination products); AND

(c) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND
Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

iv. Medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders; OR

F) Patient Currently Receiving Leqvio. Approve if according to the prescribing physician, the patient has experienced a response to therapy.
Note: Examples of a response to therapy include decreasing LDL-C, total cholesterol, non-high-density lipoprotein (non-HDL-C), or apolipoprotein B levels. Also, if the patient is currently receiving the requested therapy but has not previously received approval of Leqvio for this specific indication through the Coverage Review Department, review under criteria for Initial Therapy. If the patient is restarting therapy with Leqvio, Initial Therapy criteria must be met.

Note:
* A patient may have a diagnoses that pertains to more than one indication, therefore, consider review under different approval conditions, if applicable (e.g., a patient with heterozygous familial hypercholesterolemia may have had a clinical ASCVD event, a patient with primary hyperlipidemia may have heterozygous familial hypercholesterolemia).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Leqvio is not recommended in the following situations:

62. Concurrent use of Leqvio with Repatha (evolocumab subcutaneous injection) or Praluent (alirocumab subcutaneous injection). Repatha and Praluent are PCSK9 inhibitors and should not be used with Leqvio due to a similar mechanism of action.[1] Patients receiving PCSK9 inhibitors were excluded from the pivotal trials with Leqvio.

63. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX A

Simon Broome Register Diagnostic Criteria.[9]
LDL-C – Low-density lipoprotein cholesterol; LDL – Low-density lipoprotein; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

APPENDIX B.

Dutch Lipid Network Criteria.[8]

LDL-C – Low-density lipoprotein cholesterol; CAD – Coronary artery disease; LDLR – Low-density lipoprotein receptor; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

PRIOR AUTHORIZATION POLICY

POLICY: Psychiatry – Spravato Prior Authorization Policy
- Spravato® (esketamine nasal spray – Janssen)

REVIEW DATE: 04/19/2023

OVERVIEW

Spravato, a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist, is indicated in conjunction with an oral antidepressant for the treatment of:[1]

- Depressive symptoms in adults with **major depressive disorder (MDD) with acute suicidal ideation or behavior**.
- **Treatment-resistant depression** (TRD) in adults.

Limitation of Use: The effectiveness of Spravato in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of Spravato does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of Spravato. Spravato is not approved as an anesthetic agent. The safety and effectiveness of Spravato as an anesthetic agent have not been established.

Spravato should be administered in conjunction with an oral antidepressant.[1] For MDD with acute suicidal ideation or behavior, the recommended dosage is 84 mg twice weekly for 4 weeks. The dosage may be reduced to 56 mg twice weekly based on tolerability. After 4 weeks of treatment, evidence of therapeutic benefit should be evaluated to determine the need for continued treatment. The use of Spravato, in conjunction with an oral antidepressant, beyond 4 weeks has not been systematically evaluated in the treatment of depressive symptoms in patients with MDD with acute suicidal ideation or behavior. For treatment-resistant depression, the recommended dose is 56 mg intranasally on Day 1, followed by 56 mg or 84 mg intranasally twice weekly for Weeks 1 to 4. On Weeks 5 to 8, Spravato should be administered once weekly at a dose of 56 mg or 84 mg intranasally. On Week 9 and thereafter, the dosing frequency should be individualized to the least frequent dosing to maintain remission/response (either every 2 weeks or once weekly) at a dose of 56 mg or 84 mg. Spravato must be administered under the direct supervision of a healthcare provider.

Disease Overview

Major depressive disorder is a serious, life-threatening condition with high rates of morbidity and a chronic disease course.[2] Major depressive disorder is considered the leading cause of disability worldwide and is also associated with increased mortality rates.[3,4] About 30% to 40% of patients with major depressive disorder fail to respond to first-line treatments including oral antidepressant medications of all classes (e.g., selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], tricyclic antidepressants [TCAs], bupropion) and/or psychotherapy.[2,5] In addition, the onset of treatment response for these modalities, even when effective, often takes ≥ 4 weeks, leading to greater suffering, expense, and risk. For regulatory purposes, the FDA considers patients to have treatment-resistant depression if they have MDD and they have not responded to treatment despite trials of at least two antidepressants given at adequate doses for an adequate duration in the current episode.[2]

The available treatments for treatment-resistant depression are limited.[2] Prior to the approval of Spravato, only one medication was FDA-approved for treatment-resistant depression, Symbyax® (olanzapine and fluoxetine capsules). Symbyax is indicated for treatment-resistant depression (major depressive disorder

in patients who do not respond to two separate trials of different antidepressants of adequate dose and duration in the current episode) and acute depressive episodes in bipolar I disorder.[6]

Guidelines

According to the American Psychiatric Association practice guideline for the treatment of patients with major depressive disorder (2010), the effectiveness of antidepressants is generally comparable between classes and within classes.[7] Therefore, the initial selection of antidepressant will largely be based on the anticipated side effects, the safety or tolerability of these side effects for the individual patient, pharmacological properties of the medication (e.g., half-life, drug interactions), and additional factors such as medication response in prior episodes, cost, and patient preference. In patients with depression who either have not responded or have had trouble tolerating one SSRI agent, a trial of another SSRI (or another antidepressant) may be effective and/or better tolerated. Patients who have had a partial response to antidepressant monotherapy can be augmented with another antidepressant from a different pharmacological class or with another non-antidepressant medication, such as lithium, thyroid hormone, an anticonvulsant, a psychostimulant, or an atypical antipsychotic.

Abuse and Misuse

Spravato contains esketamine, a Schedule III controlled substance (CIII), which may be subject to abuse and diversion.[1] Assess each patient's risk for abuse or misuse prior to prescribing Spravato. All patients receiving Spravato should be monitored for the development of these behaviors or conditions, including drug-seeking behavior, while on therapy. Patients with a history of drug abuse or dependence are at greater risk. Careful consideration should be given prior to prescribing Spravato to individuals with a history of substance use disorder.

Safety

Spravato labeling includes a Boxed Warning regarding sedation, dissociation, abuse and misuse, and suicidal thoughts and behaviors in pediatric and young adult patients.[1] The most common psychological effects of Spravato were dissociative or perceptual changes (including distortion of time, space and illusions), derealization and depersonalization (61% to 84% of patients treated with Spravato developed dissociative or perceptual changes based on the Clinician-Administered Dissociative States Scale). Given its potential to induce dissociative effects, carefully assess patients with psychosis before administering Spravato; treatment should be initiated only if the benefit outweighs the risk.

Because of the risks of serious adverse outcomes resulting from sedation, dissociation, and abuse and misuse, Spravato is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).[1] Healthcare settings must be certified in the program and ensure that Spravato is only dispensed in healthcare settings and administered to patients who are enrolled in the program, administered by patients under the direct observation of a healthcare provider, and that patients are monitored by a healthcare provider for at least 2 hours after administration of Spravato. Pharmacies must be certified in the REMS and must only dispense Spravato to healthcare settings that are certified in the program.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Spravato. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Spravato as well as the monitoring required for adverse events and efficacy, approval requires Spravato to be prescribed by a physician who specializes in the condition being treated.

Note: A 2-month approval duration is applied for the indication of MDD with Acute Suicidal Ideation or Behavior to allow time for the scheduling and administration of a 4-week course of therapy at a certified

healthcare setting. If after completing the 4-week course of therapy for MDD with Acute Suicidal Ideation or Behavior, another request for Spravato is submitted and the patient meets the approval criteria, then another 4-week course of treatment (with a 2-month approval duration to complete the course of therapy) could be approved.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Spravato is recommended in those who meet one of the following criteria:

FDA-Approved Indications

4. **Major Depressive Disorder with Acute Suicidal Ideation or Behavior.** Approve for 2 months if the patient meets the following criteria (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has major depressive disorder that is considered to be severe, according to the prescriber; AND
   - **C)** Patient is concomitantly receiving at least one oral antidepressant; AND
     Note: Antidepressants may include, but are not limited to, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), mirtazapine, and bupropion.
   - **D)** Patient has one of the following (i or ii):
     - **i.** No history of psychosis; OR
     - **ii.** History of psychosis and the prescriber believes that the benefits of Spravato outweigh the risks; AND
   - **E)** The medication is prescribed by a psychiatrist.

5. **Treatment-Resistant Depression.** Approve for 6 months if the patient meets the following criteria (A, B, C, D, E, and F):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets both of the following (i and ii):
     - **i.** Patient has demonstrated nonresponse (≤ 25% improvement in depression symptoms or scores) to at least two different antidepressants, each from a different pharmacologic class, according to the prescriber; AND
       Note: Different pharmacologic classes of antidepressants include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), bupropion, mirtazapine, etc.
     - **ii.** Each antidepressant was used at therapeutic dosages for at least 6 weeks in the current episode of depression, according to the prescriber; AND
   - **C)** Patient is concomitantly receiving at least one oral antidepressant; AND
     Note: Antidepressants may include, but are not limited to, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), mirtazapine, and bupropion.
   - **D)** Patient has one of the following (i or ii):
     - **i.** No history of psychosis; OR
     - **ii.** History of psychosis and the prescriber believes that the benefits of Spravato outweigh the risks; AND
   - **E)** The patient's of controlled substance prescriptions has been checked using the state prescription drug monitoring program (PDMP), according to the prescriber; AND

F) The medication is prescribed by a psychiatrist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Spravato is not recommended in the following situations:

64. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Psychiatry – Zulresso Prior Authorization Policy
- Zulresso® (brexanolone intravenous infusion – Sage Therapeutics)

REVIEW DATE: 06/07/2023

OVERVIEW

Zulresso, a neuroactive steroid gamma-aminobutric acid (GABA) A receptor positive modulator, is indicated for the **treatment of postpartum depression in patients ≥ 15 years of age**.[1]

Disease Overview

Postpartum (or peripartum) depression is a major depressive episode with onset during pregnancy or within 4 weeks of delivery that can have serious effects on the maternal-infant bond and later infant development.[3] Approximately 40% to 80% of cases of postpartum depression are considered moderate to severe.[2]

Clinical Efficacy

The efficacy of Zulresso was established in two Phase III, US-only, randomized, double-blind, placebo-controlled, multicenter, pivotal studies in patients with moderate to severe postpartum depression initiating treatment within 6 months of delivery.[2] Eligible patients were diagnosed with a major depressive episode, which had an onset no earlier than the third trimester of pregnancy and no later than 4 weeks after delivery.

Safety

Based on findings from animal studies of other drugs that enhance GABAergic inhibition, Zulresso may cause fetal harm.[1] Currently, there are no available data on Zulresso use in pregnant women to determine a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. A pregnancy exposure registry is available to monitor pregnancy outcomes in women exposed to antidepressants during pregnancy.

Zulresso has a Boxed Warning regarding excessive sedation and sudden loss of consciousness.[1] Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their children. During the infusion, patients must be monitored for sedative effects every 2 hours during planned non-sleep periods. If there are signs or symptoms of excessive sedation, the infusion must be stopped immediately. After symptom resolution, the infusion may be restarted at the same or a lower dose. Due to the risks of serious adverse events resulting from excessive sedation and sudden loss of consciousness, Zulresso is only available through a restricted distribution system under a Risk Evaluation and Mitigation Strategy program.[1,5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zulresso. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zulresso as well as the monitoring required for adverse events and long-term efficacy, approval requires Zulresso to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Note: A 1-month (30 days) approval duration is applied to allow for the scheduling and administration of the one-time, 60-hour infusion of Zulresso.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zulresso is recommended in those who meet the following criteria:

FDA-Approved Indication

6. Postpartum Depression. Approve for 1 month if the patient meets the following criteria (A, B, C, D, and E):
- **A)** Patient is ≥ 15 years of age; AND
- **B)** Patient has been diagnosed with moderate to severe depression with symptom onset during the third trimester of pregnancy or up to 4 weeks post-delivery; AND
- **C)** Patient is ≤ 6 months postpartum; AND
- **D)** Patient is not currently pregnant; AND
- **E)** Zulresso is being prescribed by or in consultation with a psychiatrist or an obstetrician-gynecologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zulresso is not recommended in the following situations:

65. Previous Treatment with Zulresso during the Current Episode of Postpartum Depression.

66. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Psychiatry – Zurzuvae Prior Authorization Policy
- Zurzuvae™ (zuranolone capsules – Sage Therapeutics/Biogen)

REVIEW DATE: 11/15/2023

OVERVIEW

Zuranolone, a neuroactive steroid gamma-aminobutric acid (GABA) A receptor positive modulator, is indicated for the **treatment of postpartum depression in adults**.[1]

Disease Overview

Postpartum (or peripartum) depression is a major depressive episode with onset during pregnancy or within 4 weeks of delivery that can have serious effects on the maternal-infant bond and later infant development.[3] Approximately 40% to 80% of cases of postpartum depression are considered moderate to severe.[2]

Clinical Efficacy

The efficacy of Zurzuvae was established in two Phase III, randomized, double-blind, placebo-controlled, multicenter, pivotal studies in patients with severe postpartum depression initiating treatment within 6 or 12 months of delivery.[2,3] Eligible patients were diagnosed with a major depressive episode, which had an onset no earlier than the third trimester of pregnancy and no later than 4 weeks after delivery.

Safety

Based on findings from animal studies, Zurzuvae may cause fetal harm.[1] Pregnant women should be advised of the potential risk to a fetus. Available data on Zurzuvae use in pregnant women from the clinical development program are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including Zurzuvae, during pregnancy.

Zurzuvae has a Boxed Warning regarding impairment in driving or engaging in other potentially hazardous activities due to central nervous system (CNS) depressant effects.[1] Warnings/Precautions for Zurzuvae also include suicidal thoughts and behaviors (which is similar to other antidepressants) and embryo-fetal toxicity.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zurzuvae. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zurzuvae as well as the monitoring required for adverse events and long-term efficacy, approval requires Zurzuvae to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zurzuvae is recommended in those who meet the following criteria:

FDA-Approved Indication

7. **Postpartum Depression.** Approve for 14 days if the patient meets the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets BOTH of the following (i and ii):
     - **i.** Patient has been diagnosed with severe depression; AND
     - **ii.** Symptom onset began during the third trimester of pregnancy or up to 4 weeks post-delivery; AND
   - **C)** Patient is ≤ 12 months postpartum; AND
   - **D)** Patient is not currently pregnant; AND
   - **E)** Zurzuvae is being prescribed by or in consultation with a psychiatrist or an obstetrician-gynecologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zurzuvae is not recommended in the following situations:

67. **Previous Treatment with Zurzuvae during the Current Episode of Postpartum Depression**.

68. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary – Corticosteroid/Long-Acting Beta$_2$-Agonist Combination Inhalers Prior Authorization Policy

- Advair Diskus® (fluticasone propionate/salmeterol inhalation powder – GlaxoSmithKline, generic [including Wixela Inhub®])
- Advair® HFA (fluticasone propionate/salmeterol inhalation aerosol – GlaxoSmithKline, generic)
- AirDuo® Digihaler™ (fluticasone propionate/salmeterol inhalation powder – Teva)
- AirDuo® RespiClick® (fluticasone propionate/salmeterol inhalation powder – Teva, generic)
- Breo® Ellipta® (fluticasone furoate/vilanterol inhalation powder – GlaxoSmithKline; generic)
- Dulera® (mometasone furoate/formoterol fumarate inhalation aerosol – Merck)
- Symbicort® (budesonide/formoterol fumarate inhalation aerosol – AstraZeneca, generic [including Breyna™])

REVIEW DATE: 08/16/2023

OVERVIEW

The inhaled corticosteroid (ICS)/long-acting beta$_2$-agonist (LABA) combination inhalers are indicated for the treatment of asthma.[1-6] Age indications vary by agent. Fluticasone propionate and salmeterol inhalation powder (Advair Diskus, generics [including Wixela Inhub]), Breo Ellipta, and Symbicort (and authorized generic) are also indicated for the maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive lung disease (COPD), including chronic bronchitis and/or emphysema.[1,3,5] Advair HFA (and authorized generic) and Dulera are not FDA-approved for the treatment of COPD; however, both products have been studied for this use.[2,4,7-9] AirDuo Digihaler and AirDuo RespiClick (and authorized generic) also have not specifically been studied in patients with COPD. However, these agents were filed as a New Drug Application under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.[6] This approval pathway relies in part upon evidence not developed by the applicant. In the case of these agents, the literature and safety and effectiveness evidence supporting the approval and use of Advair Diskus (indicated in patients with COPD) are considered part of the evidence supporting the approval and use of the AirDuo products. Of note, another ICS/LABA inhaler, Symbicort Aerosphere® (budesonide/formoterol fumarate inhalation aerosol), was approved in 2023 for the maintenance treatment of patients with COPD. However, the manufacturer currently has no plans to launch this product in the US and this product is not targeted in this policy.

Guidelines

The 2023 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for the diagnosis, management, and prevention of COPD support the use of combination ICS/LABA therapy in select highly symptomatic patients who are at high risk for COPD exacerbations.[10] The ICS/LABAs are also featured prominently in the 2023 Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention. They are recommended as part of the step-wise treatment algorithm for patients ≥ 6 years of age.[29] European Respiratory Society (ERS) guidelines on the diagnosis and treatment of chronic cough in adults and children (2020) recommend a short-term trial (2 to 4 weeks) of ICS and long-acting bronchodilator (e.g. a

LABA) combination in adults with chronic cough and fixed airflow obstruction.[30]

Other Uses with Supportive Evidence

There are also data to support the use of ICS/LABA inhalers in patients with postinfectious cough. Subacute postinfectious cough may have multiple possible underlying etiologies, including asthma.[11,12] The underlying cause of the cough must be determined before making therapeutic decisions. In this situation, ICS/LABA combination therapy may be used as diagnostic empiric therapy in determining the cause of cough (i.e., rule out asthma). When a patient with subacute cough presents with wheezes, rhonchi, or crackles with a normal chest radiograph, it may be a reasonable option to consider therapy with an inhaled bronchodilator and ICS. If cough following an upper respiratory tract infection persists for > 8 weeks, diagnoses other than postinfectious cough should be considered.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of the Corticosteroid/Long-Acting Beta$_2$-Agonist Inhalers. The purpose of this policy is to support the use of the corticosteroid/long-acting beta$_2$-agonist combination inhalers in chronic conditions where the products are indicated or their use is appropriate. All approvals are provided for the duration listed below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: Prescription claims (prior 130 days) for respiratory medications (e.g., leukotriene receptor antagonists; xanthines; inhaled mast cell stabilizers; oral and inhaled beta-agonists; inhaled corticosteroids, inhaled anticholinergic agents) are used as a surrogate marker for a diagnosis of asthma or chronic obstructive pulmonary disease (COPD). If use of these medications is not met at the point-of-service, coverage will be determined by prior authorization criteria. When available, the ICD-10 codes for asthma and COPD (including chronic bronchitis/emphysema) will also be used in automation to generate an approval of the requested medication (see Appendix A).

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of the Corticosteroid/Long-Acting Beta$_2$-Agonist Inhalers is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Asthma/Reactive Airway Disease.** Approve for 1 year.

2. **Chronic Obstructive Pulmonary Disease.** Approve for 1 year.

3. **Chronic Bronchitis.** Approve for 1 year.

4. **Emphysema.** Approve for 1 year.

Other Uses with Supportive Evidence

5. **Postinfectious Cough.** Approve for 2 months.
   Note: Postinfectious cough is cough that persists after an acute respiratory infection has resolved.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of the Corticosteroid/Long-Acting Beta$_2$-Agonist Inhalers is not recommended in the following situations:

57. **Acute Cough Associated with the Common Cold.** Note: This includes symptoms associated with a current rhinovirus infection.
    There are no data to support the use of ICS/LABA combination therapy in treating this condition. American College of Chest Physicians (ACCP) guidelines for the treatment of acute cough associated with the common cold do not recommend using an ICS or a bronchodilator in treating this condition.[11,26]

58. **Chronic Cough due to Gastroesophageal Reflux Disease (GERD).** There are no data to support the use of ICS/LABA combination therapy in treating this condition. The ACCP guidelines for the management of chronic cough due to GERD recommend treatment of the underlying condition and do not mention the use of any inhaled therapies.[13,24]

59. **Acute Cough due to an Acute Respiratory Infection.** Note: Examples of an acute respiratory infection are acute bronchitis, sinusitis, influenza, or pneumonia. An acute exacerbation of chronic bronchitis is not the same as acute bronchitis.
    ACCP guidelines for the management of acute cough due to acute bronchitis in immunocompetent adult outpatients do not recommend routine use of inhaled corticosteroids and inhaled beta-agonists.[14] Current evidence is not sufficient to prove that these therapies are safe and effective at reducing the severity and duration of cough in this setting. Bronchodilators are also not a recommended therapeutic option in treating cough associated with acute bacterial sinusitis.[12] Additional ACCP guidelines for the management of acute cough due to suspected pneumonia or influenza state that there is insufficient evidence on the use of nonantibiotic symptomatic therapies such as ICSs or bronchodilators.[26] There are no data to support the use of ICS/LABA combination therapy in treating these conditions.

60. **Chronic Cough due to Non-Asthmatic Eosinophilic Bronchitis (NAEB).** There are no data to support the use of ICS/LABA combination therapy in treating this condition. Per the guidelines for the management of chronic cough due to NAEB from ACCP ICSs are the recommended first-line treatment.[11,23] One of the clinical characteristics of NAEB is chronic cough without evidence of variable airflow obstruction or airway hyperresponsiveness. As a result, a beta-agonist bronchodilator would not be expected to be useful in treating this condition.

61. **Chronic Cough due to Bronchiolitis.** The ACCP guidelines do not recommend bronchodilators as a therapeutic option in treating bronchiolitis.[11,15] Use of asthma medications is discouraged unless other evidence of asthma is present. Guidelines from the American Academy of Pediatrics regarding the diagnosis and management of bronchiolitis (2014) also do not recommend inhaled corticosteroids or bronchodilators be routinely used in the management of bronchiolitis.[16]

62. **Chronic Cough due to Bronchiectasis.** Limited data are available with budesonide/formoterol (foreign formulation of Symbicort) for the treatment of non-cystic fibrosis (CF) bronchiectasis.[17,18] ACCP guidelines note that in patients with bronchiectasis due to CF or other causes, treatment of respiratory infections and airway clearance techniques are the mainstays of management.[27] In patients with airflow obstruction and/or bronchial hyperreactivity (e.g., asthma and/or COPD), bronchodilators may be of benefit.[11,19] However, the ACCP guidelines and the British Thoracic Society (BTS) guidelines do not recommend treatment with ICSs. Bronchiectasis guidelines from the European Respiratory Society also recommend against offering ICSs to adult, adolescent, and patients with bronchiectasis.[20,32] There may be a role for combination ICS/LABA therapy in patients with coexisting

asthma or COPD, but there is no evidence to support this therapy in patients without these concomitant conditions.[19,20,32]

63. Whooping Cough/Pertussis. There are no data to support the use of ICS/LABA combination therapy in treating this condition. According to the ACCP guidelines, LABAs and corticosteroids should not be offered to patients with whooping cough as there is no evidence to suggest benefit.[11] Although short-acting beta-agonists (SABA) [along with other treatments] have been proposed as standard treatment for whooping cough, one review article reported that treatment with the SABA salbutamol resulted in no change in coughing.[21]

64. Angiotensin-Converting Enzyme (ACE) Inhibitor-Induced Cough. There are no data to support the use of ICS/LABA combination therapy in treating this condition. Discontinuation of the ACE inhibitor is the only uniformly effective treatment for ACE inhibitor-induced cough. In those patients in whom the ACE inhibitor cannot be discontinued, pharmacologic therapy aimed at suppressing cough should be attempted. ICSs and beta-agonists are not recommended therapeutic options.[11]

65. Psychogenic Cough/Habit Cough/Tic Cough. There are no data to support the use of ICS/LABA combination therapy in treating these conditions. Non-pharmacological therapies, such as behavior modification, hypnosis and psychiatric therapy are the mainstays of treatment.[11,22]

66. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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NA – Not applicable.

APPENDIX A

ICD-10 Codes Automated for Asthma and COPD

COPD – Chronic obstructive pulmonary disease; * Indicates the inclusion of subheadings.

PRIOR AUTHORIZATION WITH STEP THERAPY POLICY

POLICY: Pulmonary – Roflumilast Prior Authorization with Step Therapy Policy
- Daliresp® (roflumilast tablets – Astra Zeneca, generic)

REVIEW DATE: 01/11/2023

OVERVIEW

Roflumilast tablets (Daliresp, generic), a selective phosphodiesterase-4 inhibitor, is indicated as a treatment to reduce the risk of **chronic obstructive pulmonary disease** (COPD) exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.[1] Limitations of use: Roflumilast is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

Clinical Efficacy

Roflumilast has been studied in patients currently receiving treatment with bronchodilators (e.g., long-acting beta$_2$-agonists [LABAs]) and inhaled corticosteroids (ICSs) with or without additional therapy with a long-acting muscarinic antagonist (LAMA).[2-7] Five placebo-controlled clinical trials evaluated the effect of roflumilast on COPD exacerbations.[1-7] Two of these studies initially included patients with severe COPD with chronic bronchitis and/or emphysema; in both studies, roflumilast did not demonstrate a significant reduction in COPD exacerbation rates. An exploratory analysis of these trials found that in the subgroup of patients with severe COPD who had chronic bronchitis and exacerbations within the previous year, roflumilast resulted in better exacerbation reduction than in the overall population. Two subsequent trials were conducted involving patients with severe COPD, chronic bronchitis, and at least one COPD exacerbation within the previous year. In both trials, roflumilast demonstrated a significant reduction in the rate of moderate or severe exacerbations compared to placebo.

Guidelines

The Global Initiative for Chronic Obstructive Lung Disease guidelines for the diagnosis, management, and prevention of COPD (2023) recommend bronchodilators as initial pharmacologic treatment.[8] Following initiation, therapies should be adjusted as needed based on symptom severity and exacerbation risk. ICSs are recommended for patients who continue to experience COPD exacerbations and who have elevated blood eosinophils. Roflumilast is listed as a possible therapeutic option in patients with chronic bronchitis who are receiving triple therapy with an ICS/LAMA/LABA, who have a forced expiratory volume in 1 second (FEV_1) < 50%, and who continue to experience exacerbations (especially if the patient has been hospitalized for one or more COPD exacerbations in the past year). This therapy is also recommended in patients who continue to experience exacerbations despite LAMA/LABA combination therapy and have a blood eosinophil level < 100 cells/microliter. Low blood eosinophils are predictive of an insufficient response to ICS therapy, thereby making roflumilast a more attractive option for add-on therapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of roflumilast tablets (Daliresp, generic). This Prior Authorization Policy also contains a Step Therapy component. When clinically appropriate, the patient is directed to try generic roflumilast (Step 1) prior to brand Daliresp (Step 2). All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of roflumilast tablets (Daliresp, generic) is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Chronic Obstructive Pulmonary Disease (COPD).** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
   - **A)** Patient has severe COPD or very severe COPD, according to the prescriber; AND
   - **B)** Patient has a of exacerbations; AND
   - **C)** Patient meets ONE of the following (i or ii):
   - **i.** Patient meets both of the following (a and b):
     - **a)** Patient has chronic bronchitis; AND
     - **b)** Patient has tried an inhaled long-acting beta$_2$-agonist, an inhaled long-acting muscarinic antagonist, and an inhaled corticosteroid concomitantly; OR
       WW) Note: Use of a combination inhaler containing multiple agents from the medication classes listed would fulfil the requirement. Refer to the **Appendix** for examples of inhaled therapies used for COPD.
   - **ii.** Patient meets both of the following (a and b):
     - **a)** Patient has a blood eosinophil level < 100 cells/microliter; AND
     - **b)** Patient has tried an inhaled long-acting muscarinic antagonist and long-acting beta$_2$-agonist concomitantly.
       Note: Use of a combination inhaler containing multiple agents from the medication classes listed would fulfil the requirement. Refer to the **Appendix** for examples of inhaled therapies used for COPD.
   - **D)** If brand Daliresp is being requested, the patient meets both of the following criteria (i and ii):
   - **i.** Patient has tried generic roflumilast; AND
   - **ii.** Brand Daliresp is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of roflumilast tablets (Daliresp, generic) is not recommended for the following situations:

67. **Asthma.** The efficacy of roflumilast (formulation not specified) in patients with asthma[9-11], allergic asthma[12,13], and exercise-induced asthma[14] has been evaluated. More data are needed to define the place in therapy of roflumilast in the treatment of asthma. Current asthma guidelines do not address roflumilast as a recommended therapy for asthma management.[15-17]

68. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

LABA – Long-acting beta$_2$-agonist; LAMA – Long-acting muscarinic antagonist; ICS – Inhaled corticosteroid.

PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Adempas Prior Authorization Policy
- Adempas® (riociguat tablets – Bayer)

REVIEW DATE: 10/11/2023

OVERVIEW

Adempas, a soluble guanylate cyclase stimulator, is indicated for the treatment of adults with:[1]

- **Chronic thromboembolic pulmonary hypertension** (CTEPH) [World Health Organization {WHO} Group 4], persistent/recurrent, after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class.
- **Pulmonary Arterial Hypertension** (PAH) [WHO Group 1], to improve exercise capacity, WHO functional class, and to delay clinical worsening.

Disease Overview

PAH is a serious but rare condition impacting fewer than 20,000 patients in the US.[2,3] It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized. In this progressive disorder, the small arteries in the lungs become narrowed, restricted, or blocked causing the heart to work harder to pump blood, leading to activity impairment.[2,3] Although the mean age of diagnosis is between 36 and 50 years, patients of any age may be affected, including pediatric patients. PAH is defined as a mean pulmonary artery pressure (mPAP) > 20 mmHg (at rest) with a pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg and a pulmonary vascular resistance > 2 Wood units measured by cardiac catheterization.[7] The prognosis in PAH has been described as poor, with the median survival being approximately 3 years. However, primarily due to advances in pharmacological therapies, the long-term prognosis has improved.

CTEPH is a persistent obstruction of pulmonary arteries and is often a complication of pulmonary embolism.[4,5] It is classified within WHO Group 4 pulmonary hypertension. Symptoms include progressive dyspnea on exertion, as well as fatigue, syncope, hemoptysis, and signs of right heart failure. Pulmonary endarterectomy is the treatment of choice for most patients with CTEPH. However, around 40% of patients are deemed inoperable for various reasons. Medication therapy, including Adempas, may also be recommended. Anticoagulant therapy is also given.

Guidelines

Various guidelines are available for the management of pulmonary hypertension.

- **Pulmonary Arterial Hypertension:** The CHEST guideline and Expert Panel Report regarding therapy for PAH in adults (2019) cites Adempas as a vital therapy with several benefits in a variety of clinical scenarios. The European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines regarding the treatment of pulmonary hypertension (2022) also recognize Adempas as having a prominent role in the management of this condition, as monotherapy or in combination with other agents.
- **Chronic Thromboembolic Pulmonary Hypertension:** Guidelines from the ESC/ERS regarding the treatment of pulmonary hypertension (2022) recommended Adempas for patients who are symptomatic with inoperable CTEPH or persistent/recurrent pulmonary hypertension after pulmonary endarterectomy.[6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Adempas. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Adempas as well as the monitoring required for adverse events and long-term efficacy, approval requires Adempas to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for initiation of therapy where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and catheterization laboratory reports. For a patient case in which the documentation requirement of the right heart catheterization upon Prior Authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this *Pulmonary Arterial Hypertension – Adempas Prior Authorization Policy* is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Adempas is recommended in those who meet one of the following criteria:

FDA-Approved Indications

17. **Chronic Thromboembolic Pulmonary Hypertension.** Approve for 1 year if prescribed by or in consultation with a pulmonologist or a cardiologist.

18. **Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1].** Approve for the duration noted if the patient meets ONE of the following (A or B):
    - **A)** Initial Therapy. Approve for 1 year if the patient meets all of the following (i, ii, and iii):
        - **i.** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
        - **ii.** Patient meets the following (a and b):
            - Patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND
            - Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
        - **iii.** Medication is prescribed by or in consultation with a cardiologist or a pulmonologist.
    - **B)** Patient is Currently Receiving Adempas. Approve for 1 year if the patient meets all of the following (i ii, and iii):
        - **i.** Patient has a diagnosis of WHO Group 1 PAH; AND
        - **ii.** Patient meets the following (a and b):
            - **a)** Patient has had a right heart catheterization; AND
            - **b)** Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
        - **iii.** Medication is prescribed by or in consultation with a cardiologist or a pulmonologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Adempas is not recommended in the following situations:

1. **Concurrent Use with Phosphodiesterase Inhibitors Used for Pulmonary Hypertension or Other Soluble Guanylate Cyclase Stimulators.** Use of Adempas with phosphodiesterase inhibitors and/or with other soluble guanylate cyclase stimulators is a contraindication.[1]
   Note: Examples of phosphodiesterase inhibitors used for pulmonary hypertension include Revatio (sildenafil tablets, suspension, and intravenous injection), Adcirca (tadalafil tablets), Alyq (tadalafil tablets), and Tadliq (tadalafil oral suspension). An example of a soluble guanylate cyclase stimulator is Verquvo (vericiguat tablets).

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Endothelin Receptor Antagonists
- Letairis® (ambrisentan tablets – Gilead, generic)
- Opsumit® (macitentan tablets – Actelion/Janssen)
- Tracleer® (bosentan tablets and tablets for oral suspension – Actelion/Janssen, generic for tablets)

REVIEW DATE: 10/04/2023

OVERVIEW

Ambrisentan (Letairis, generic), Opsumit, and bosentan (Tracleer, generic [generic for tablets only]), oral endothelin receptor antagonists, are indicated for the treatment of **pulmonary arterial hypertension** (PAH), World Health Organization (WHO) Group 1.[1-3]

- Ambrisentan is indicated to improve exercise ability and delay clinical worsening as well as for use in combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.[2]
- Opsumit is noted to reduce the risks of disease progression and hospitalization for PAH.[3]
- Bosentan is indicated in adults to improve exercise ability and decrease the rate of clinical worsening and in pediatric patients ≥ 3 years of age with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability.[1]

The BENEFiT (Bosentan Effects in iNopErable Forms of chronic Thromboembolic pulmonary hypertension) study was a double-blind trial involving patients with chronic thromboembolic pulmonary hypertension (CTEPH) who were randomized to Tracleer or placebo for 16 weeks (n = 156). Benefits were noted in some hemodynamic parameters (e.g., decreased PVR).[4] Adempas® (riociguat tablets), a soluble guanylate cyclase stimulator, is the only agent indicated for the treatment of adults with CTEPH (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class.[5] The agent is also indicated for the treatment of adults with PAH (WHO Group 1). Adempas has a Boxed Warning regarding embryofetal toxicity and is contraindicated in patients using nitrates or nitric oxide donors in any forms, as well as in patients using phosphodiestase inhibitors. The main adverse event associated with Adempas is symptomatic hypotension.

Tracleer has been used in patients with systemic sclerosis who have digital ulcers.[6-13] In a prospective, multicenter, placebo-controlled, double-blind study patients (n = 122) with limited or diffuse systemic sclerosis (scleroderma) were randomized in a 2:1 ratio to receive Tracleer or placebo for 16 weeks.[6] Patients receiving Tracleer had a 48% reduction in the mean number of new ulcerations (1.4 vs. 2.7 new ulcers; P = 0.0083), the primary efficacy endpoint. The effect was more substantial in patients with digital ulcers at study entry. However, no differences were noted in the healing of established ulcers.[6] Another trial showed a reduction in the occurrence of new digital ulcers in patients given Tracleer for 24 weeks.[10]

Disease Overview

PAH is a serious but rare condition impacting fewer than 20,000 patients in the US.[14,15] It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized. In this progressive disorder, the small arteries in the lungs become narrowed, restricted, or blocked causing the heart to work harder to pump blood, leading to activity impairment. Although the mean age of diagnosis is between 36 and 50 years, patients of any age may be affected, including pediatric patients. PAH is

defined as a mean pulmonary artery pressure (mPAP) > 20 mmHg (at rest) with a pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg and a pulmonary vascular resistance > 2 Wood units measured by cardiac catheterization.[19] The prognosis in PAH has been described as poor, with the median survival being approximately 3 years. However, primarily due to advances in pharmacological therapies, the long-term prognosis has improved.

CTEPH is a persistent obstruction of pulmonary arteries and is often a complication of pulmonary embolism.[16,17] It is classified within Group 4 pulmonary hypertension. Symptoms include progressive dyspnea on exertion, as well as fatigue, syncope, hemoptysis, and signs of right heart failure. Pulmonary endarterectomy is the treatment of choice for most patients with CTEPH. However, around 40% of patients are deemed inoperable for various reasons. Medication therapy may also be recommended. Anticoagulant therapy is also given.

Guidelines

Various guidelines address endothelin receptor antagonists.

- **Pulmonary Arterial Hypertension (PAH):** The CHEST guideline and Expert Panel Report regarding therapy for PAH (2019) in adults details many medications. It was noted that endothelin receptor antagonists play a vital role and have various benefits in the management of PAH.[15] The European Society of Cardiology and the European Respiratory Society guidelines regarding the treatment of pulmonary hypertension (2022) also recognize endothelin receptor antagonists as having a prominent role in the management of this condition, as monotherapy or in use as combination with other agents.[18]
- **Systemic Sclerosis:** In 2017, the European League Against Rheumatism (EULAR) updated recommendations for the treatment of systemic sclerosis.[12] Tracleer should be considered to reduce the number of new digital ulcers in systemic sclerosis, especially in patients who have multiple digital ulcers despite use of calcium channel blockers, phosphodiesterase type 5 inhibitors or iloprost therapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of ambrisentan, Opsumit, and bosentan. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with these agents, as well as the monitoring required for adverse events and long-term efficacy, approval requires the agents to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for initiation of therapy as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and catheterization laboratory reports. For a patient case in which the documentation requirement of the right heart catheterization upon Prior Authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this *Pulmonary Arterial Hypertension – Endothelin Receptor Antagonist Prior Authorization Policy* is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of ambrisentan (Letairis, generic), Opsumit, and bosentan (Tracleer, generic) is recommended in those who meet the following criteria:

FDA-Approved Indication

19. Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1]. Approve for the duration noted if the patient meets ONE of the following (A or B):

C) Initial Therapy. Approve for 1 year if the patient meets all of the following (i , ii, and iii).

i. Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

ii. Patient meets the following (a and b):

a) Patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND

b) Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

iii. The medication is prescribed by or in consultation with a cardiologist or a pulmonologist.

D) Patient is Currently Receiving the Requested Endothelin Receptor Antagonist (i.e., ambrisentan [Letairis, generic], Opsumit, or bosentan [Tracleer, generic]). Approve for 1 year if the patient meets the following (i, ii, and iii):

iv. Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

v. Patient meets the following (a and b):

a) Patient has had a right heart catheterization; AND

b) Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

vi. The medication is prescribed by or in consultation with a cardiologist or a pulmonologist.

Other Uses with Supportive Evidence

Coverage of bosentan (Tracleer, generic) is also recommended in those who meet the following criteria:

20. Chronic Thromboembolic Pulmonary Hypertension (CTEPH). Approve Tracleer for 1 year if the patient meets the following (A and B):

A) Patient meets one of the following (i, ii, or iii):

i. Patient has tried Adempas; OR

ii. According to the prescriber, use of Adempas is contraindicated; OR

Note: Examples of contraindications to use of Adempas include that the patient is receiving nitrates or nitric oxide donors, the patient is receiving a phosphodiesterase inhibitor such as sildenafil or tadalafil, or that the patient is hypotensive or is at risk for hypotension.

iii. Patient is currently receiving Tracleer.

B) The medication is prescribed by or in consultation with a cardiologist or a pulmonologist.

21. Digital Ulcers in a Patient with Systemic Sclerosis. Approve Tracleer for 1 year if the patient meets ONE of the following (A or B):

A) Patient has tried one calcium channel blocker; OR

Note: Examples include amlodipine, felodipine and nifedipine.

B) Patient has tried one phosphodiesterase type 5 (PDE5) inhibitor.

Note: Examples include sildenafil, tadalafil and vardenafil.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of ambrisentan, Opsumit, and bosentan is not recommended in the following situations:

69. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Epoprostenol Products Prior Authorization Policy
- Flolan® (epoprostenol intravenous infusion – GlaxoSmithKline, generic)
- Veletri® (epoprostenol intravenous infusion – Actelion/Janssen)

REVIEW DATE: 10/04/2023

OVERVIEW

Epoprostenol intravenous infusion, a prostacyclin vasodilator, is indicated for the treatment of pulmonary arterial hypertension (PAH) [World Health Organization {WHO} Group 1] to improve exercise capacity.[1-3]

Epoprostenol injection has been used with varying results in patients with chronic thromboembolic pulmonary hypertension (CTEPH).[4-6] It is sometimes used as a bridge prior to surgery. Limited options are available for patients with CTEPH.

Disease Overview

PAH is a serious but rare condition impacting fewer than 20,000 patients in the US.[7,8] The estimated incidence of PAH is 2 cases per 1 million per year with a prevalence of 10.6 cases per 1 million adults.[7] It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized.[7,8] In this progressive disorder, the small arteries in the lungs become narrowed, restricted, or blocked causing the heart to work harder to pump blood, leading to activity impairment. In time, right-sided heart failure and/or death may occur. Common PAH symptoms include shortness of breath, fatigue, chest pain, dizziness, and fainting, along with impairment in activity tolerance. It is more prevalent in women. Patients of all ages may develop the disease; however, the mean age of diagnosis typically happens between 36 to 50 years. Children may also have PAH. The condition may occur due to various underlying medical conditions (e.g., connective tissue disease, HIV) or as a disease that uniquely impacts the pulmonary circulation; both genetic and environmental factors may be involved. PAH is defined as a mean pulmonary artery pressure (mPAP) > 20 mmHg (at rest) with a pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg and a pulmonary vascular resistance > 2 Wood units measured by cardiac catheterization.[13] The prognosis in PAH has been described as poor, with the median survival being approximately 3 years. However, primarily due to advances in pharmacological therapies, the long-term prognosis has improved. Lung transplantation may be recommended if pharmacological or medical therapies fail, based upon patient status. The WHO categorizes PAH into stages, which is also referred to as the functional class (Class I to IV) and is an adaptation of the New York Heart Association system to evaluate activity tolerance.

CTEPH is a persistent obstruction of pulmonary arteries and is often a complication of pulmonary embolism.[9,10] It is classified within Group 4 pulmonary hypertension. Symptoms include progressive dyspnea on exertion, as well as fatigue, syncope, hemoptysis, and signs of right heart failure. Pulmonary endarterectomy is the treatment of choice for most patients with CTEPH. However, around 40% of patients are deemed inoperable for various reasons. Medication therapy may also be recommended. Anticoagulant therapy is also given.

Guidelines

Several guidelines address intravenous epoprostenol products in the management of pulmonary hypertension.[8,11]

- **Pulmonary Arterial Hypertension:** The CHEST guidelines and Expert Panel Report regarding therapy for PAH in adults (2019) cites the many medications that have utility for this condition.[8]

In the absence of contraindications, patients with PAH should undergo acute vasoreactivity testing utilizing a short-acting agent (e.g., calcium channel blockers). For patients in Functional Class II, oral therapies are recommended such as endothelin receptor antagonists (ambrisentan, bosentan, Opsumit® [macitentan tablets]), phosphodiesterase type 5 inhibitors (tadalafil, sildenafil), and Adempas® (riociguat tablets). It is suggest that parenteral or inhaled prostanoids not be chosen as initial therapy for treatment naïve-patients with PAH with WHO Functional Class II symptoms or as second-line agents for patients with PAH with WHO Functional Class II who have not met their treatment goals. Parenteral prostanoids are recommended for patients with PAH in Functional Class III and IV.[8] The European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines regarding the treatment of pulmonary hypertension (2022) also recognize intravenous epoprostenol as having a prominent role in the management of this condition, usually in later therapy stages and after other therapies.[11]

- **Chronic Thromboembolic Pulmonary Hypertension:** Guidelines from the ESC/ERS regarding the treatment of pulmonary hypertension (2022) recommended to consider parenteral prostacyclin analogs for patients with inoperable CTEPH.[11]

Safety

Epoprostenol should not be abruptly discontinued or have the dose rapidly decreased as rebound pulmonary hypertension may occur.[1-3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of epoprostenol injection. All approvals are provided for 1 year in duration unless otherwise noted below. Specifically, approvals will remain up to 14 days for patients currently receiving the agent for the indication of PAH (WHO Group 1) with inadequate information or if the criteria are not met. These cases are reviewed by a nurse or pharmacist. Because of the specialized skills required for evaluation and diagnosis of patients treated with epoprostenol injection as well as the monitoring required for adverse events and long-term efficacy, approval requires epoprostenol injection to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: In the *Pulmonary Arterial Hypertension – Epoprostenol Prior Authorization Policy*, documentation is required for initiation of therapy where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and catheterization laboratory reports. For a patient case in which the documentation requirement of the right heart catheterization upon prior authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this *Pulmonary Arterial Hypertension – Epoprostenol Prior Authorization Policy* is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of epoprostenol injection is recommended in those who meet one of the following criteria:

FDA-Approved Indication

22. Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1]. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 year if the patient meets all of the following (i, ii, iii, iv, and v):

i. Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

ii. Patient meets the following (a and b):

a) Patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND

b) Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

iii. Patient meets ONE of the following (a or b):

a) Patient is in Functional Class III or IV; OR

b) Patient is in Functional Class II and meets ONE of the following [(1) or (2)]:

(1) Patient has tried or is currently receiving one oral agent for PAH; OR

Note: Examples of oral agents for PAH include bosentan, ambrisentan, Opsumit (macitentan tablets), Adempas (riociguat tablets), sildenafil, tadalafil, Orenitram (treprostinil extended-release tablets), Alyq (tadalafil tablets), Tadliq (tadalafil oral suspension), and Uptravi (selexipag tablets).

(2) Patient has tried one inhaled or parenteral prostacyclin product for PAH; AND

Note: Examples of inhaled and parenteral prostacyclin products for PAH include Tyvaso (treprostinil inhalation solution), Tyvaso DPI (treprostinil oral inhalation powder), Ventavis (iloprost inhalation solution), treprostinil injection, and epoprostenol injection.

iv. Patient with idiopathic PAH must meet ONE of the following (a, b, c, d, or e):

a) Patient must meet both of the following [(1) and (2)]:

(1) According to the prescriber, the patient has had an acute response to vasodilator testing that occurred during the right heart catheterization; AND

Note: An example of a response can be defined as a decrease in mean pulmonary artery pressure of at least 10 mm Hg to an absolute mean pulmonary artery pressure of less than 40 mm Hg without a decrease in cardiac output.

(2) Patient has tried one oral calcium channel blocker (CCB) therapy; OR

Note: Examples of CCBs include amlodipine and nifedipine extended-release tablets.

b) According to the prescriber, the patient did not have an acute response to vasodilator testing; OR

c) According to the prescriber, the patient cannot undergo a vasodilator test; OR

d) Patient cannot take CCB therapy; OR

Note: Examples of reasons a patient cannot take CCB therapy include right heart failure or decreased cardiac output.

e) Patient has tried one CCB; AND

Note: Examples of CCBs include amlodipine and nifedipine extended-release tablets.

v. Medication is prescribed by or in consultation with a cardiologist or a pulmonologist; OR

B) Patient Currently Receiving Epoprostenol. Approve for the duration noted below if the patient meets one of the following (i or ii):

i. Approve for 1 year if the patient meets ALL of the following (a, b, and c):

a) Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

b) Patient meets the following [(1) and (2)]:

(1) Patient has had a right heart catheterization; AND

(2) Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

c) Medication is prescribed by or in consultation with a cardiologist or a pulmonologist; OR

ii. Approve a short-term supply of epoprostenol for up to 14 days if the patient does not meet the criteria in 1Bi above or if there is insufficient information available. All approvals are reviewed by a nurse or pharmacist.

Note: A 14-day supply should be sufficient to address coverage issues. However, multiple short-term approvals are allowed if a coverage determination cannot be made. Abrupt discontinuation of epoprostenol therapy may have severe adverse consequences.

Other Uses with Supportive Evidence

23. Chronic Thromboembolic Pulmonary Hypertension (CTEPH). Approve for 1 year if prescribed by or in consultation with a pulmonologist or a cardiologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of epoprostenol injection is not recommended in the following situations:

1. **Chronic Obstructive Pulmonary Disease (COPD) in a Patient Without PAH (WHO Group 1).** COPD is classified as Group 3 Pulmonary Hypertension (pulmonary hypertension associated with lung diseases and/or hypoxia). Pulmonary hypertension may develop late in the course of COPD, but medications used for the treatment of PAH (WHO Group 1) are not recommended therapies.[12]

2. **Concurrent Use with Parenteral Treprostinil Products, Oral Prostacyclin Products, or Inhaled Prostacyclin Agents Used for Pulmonary Hypertension.**
   Note: Examples of medications include Orenitram (treprostinil extended-release tablets), Uptravi (selexipag tablets and intravenous infusion), Tyvaso (treprostinil inhalation solution), Tyvaso DPI (treprostinil oral inhalation powder), Ventavis (iloprost inhalation solution), and treprostinil subcutaneous injection and intravenous infusion (Remodulin, generic).

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Orenitram Prior Authorization Policy
- Orenitram® (treprostinil extended-release tablets – United Therapeutics)

REVIEW DATE: 10/11/2023

OVERVIEW

Orenitram, a prostacyclin mimetic, is indicated for the treatment of **pulmonary arterial hypertension (PAH) World Health Organization (WHO) Group 1** to delay disease progression and to improve exercise capacity.[1]

Disease Overview

PAH is a serious but rare condition impacting fewer than 20,000 patients in the US.[2,3] It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized. In this progressive disorder, the small arteries in the lungs become narrowed, restricted, or blocked causing the heart to work harder to pump blood, leading to activity impairment. Although the mean age of diagnosis is between 36 and 50 years, patients of any age may be affected, including pediatric patients. PAH is defined as a mean pulmonary artery pressure (mPAP) > 20 mmHg (at rest) with a pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg and a pulmonary vascular resistance > 2 Wood units measured by cardiac catheterization.[5] The prognosis in PAH has been described as poor, with the median survival being approximately 3 years. However, primarily due to advances in pharmacological therapies, the long-term prognosis has improved.

Guidelines

Various guidelines address oral prostacyclin products.[3,4] The CHEST guideline and Expert Panel Report regarding therapy for pulmonary arterial hypertension (2019) in adults details many medications.[3] It was cited that many agents with varying mechanisms of action are used for the management of PAH. It was noted that the addition of an oral prostanoid product is recommended in patients with PAH who are in Functional Class III without evidence of rapid disease progression or a poor prognosis among those not willing or able to manage parenteral prostanoids. The European Society of Cardiology and the European Respiratory Society guidelines regarding the treatment of pulmonary hypertension (2022) also recognize Orenitram as having a role in therapy, mainly as an agent to be added onto other PAH therapies.[4]

Safety

Abrupt discontinuation or sudden large reductions in the dosage of Orenitram may cause PAH symptoms to worsen.[1] In the event of a planned short-term treatment interruption for patients unable to take oral medication, consider a temporary infusion of subcutaneous or intravenous treprostinil.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Orenitram. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Orenitram as well as the monitoring required for adverse events and long-term efficacy, approval requires Orenitram to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for initiation of therapy where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and

catheterization laboratory reports. For a patient case in which the documentation requirement of the right heart catheterization upon prior authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this *Pulmonary Arterial Hypertension – Orenitram Prior Authorization Policy* is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Orenitram is recommended in those who meet the following criteria:

FDA-Approved Indication

24. Pulmonary Arterial Hypertension (World Health Organization [WHO] Group 1). Approve for the duration noted if the patient meets ONE of the following (A or B):

E) Initial Therapy. Approve for 1 year if the patient meets all of the following (i, ii, iii, and iv):

i. Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

ii. Patient meets the following (a and b):

a) Patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND

b) Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

iii. Patient meets one of the following (a or b):

a) Patient has tried two oral therapies for PAH (or is currently receiving them) from two of the three following different categories (either alone or in combination) each for ≥ 60 days: one phosphodiesterase type 5 (PDE5) inhibitor, one endothelin receptor antagonist (ERA), or Adempas (riociguat tablets); OR

Note: Examples of phosphodiesterase type 5 inhibitors include sildenafil and tadalafil. Examples of endothelin receptor antagonists include bosentan, ambrisentan, and Opsumit (macitentan tablets).

b) Patient is receiving or has received in the past one PAH prostacyclin therapy or a prostacyclin receptor agonist (i.e., Uptravi [selexipag tablets]) for PAH; AND

Note: Examples of prostacyclin therapies for PAH include Tyvaso (treprostinil inhalation solution), Tyvaso DPI (treprostinil oral inhalation), Ventavis (iloprost inhalation solution), treprostinil injection, and epoprostenol injection.

iv. Medication is prescribed by or in consultation with a cardiologist or a pulmonologist.

F) Patient is Currently Receiving Orenitram. Approve for 1 year if the patient meets all of the following (i, ii, and iii):

vii. Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

viii. Patient meets the following (a and b):

a) Patient has had a right heart catheterization; AND

b) Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH); AND

The medication is prescribed by, or in consultation with, a cardiologist or a pulmonologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Orenitram is not recommended in the following situations:

70. Concurrent Use with Uptravi (selexipag tablets and intravenous infusion), Inhaled Prostacyclin Products, or Parenteral Prostacyclin Agents Used for Pulmonary Hypertension.
Note: Examples of medications include Tyvaso (treprostinil inhalation solution), Tyvaso DPI (treprostinil oral inhalation powder), Ventavis (iloprost inhalation solution), epoprostenol intravenous infusion, and treprostinil subcutaneous or intravenous infusion (Remodulin, generic).

71. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Phosphodiesterase Type 5 Inhibitors Prior Authorization Policy

- Adcirca® (tadalafil tablets – Eli Lilly/United Therapeutics, generic)
- Alyq™ (tadalafil tablets – Teva, generic)
- LiQrev® (sildenafil oral suspension – CMP)
- Revatio® (sildenafil tablets and suspension – Pfizer, generic)
  Note: Revatio injection is not included in this policy
- Tadliq® (tadalafil oral suspension – CMP)

REVIEW DATE: 10/11/2023

OVERVIEW

Adcirca, Alyq, LiQrev, Revatio, and Tadliq are phosphodiesterase type 5 (PDE5) inhibitors indicated for the treatment of **pulmonary arterial hypertension** (PAH).[1-4] Alyq is a generic to Adcirca.[4]

- Adcirca, Alyq, and Tadliq are indicated for the treatment of PAH (World Health Organization [WHO] Group I) to improve exercise ability.[2-4]
- Liqrev and Revatio are indicated for the treatment of PAH (WHO Group I) in adults to improve exercise ability and delay clinical worsening.[1,16]
- Revatio is also indicated in pediatric patients 1 to 17 years old for the treatment of PAH to improve exercise ability and, in pediatric patients too young to perform standard exercise testing, pulmonary hemodynamics thought to underly improvements in exercise.[1]

Tadalafil and sildenafil have some data in patients with Raynaud's phenomenon at doses provided in strengths used for PAH.[5-8] In many situations, patients also had scleroderma. Benefits were noted, such as decrease frequency and shorter durations of attacks, as well as in selected parameters regarding digital ulceration.

Disease Overview

PAH is a serious but rare condition impacting fewer than 20,000 patients in the US.[9,10] It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized. In this progressive disorder, the small arteries in the lungs become narrowed, restricted, or blocked causing the heart to work harder to pump blood, leading to activity impairment. Although the mean age of diagnosis is between 36 and 50 years, patients of any age may be affected, including pediatric patients. PAH is defined as a mean pulmonary artery pressure (mPAP) > 20 mmHg (at rest) with a pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg and a pulmonary vascular resistance > 2 Wood units measured by cardiac catheterization.[17] The prognosis in PAH has been described as poor, with the median survival being approximately 3 years. However, primarily due to advances in pharmacological therapies, the long-term prognosis has improved.

Guidelines

Various guidelines address PDE5 inhibitors for the conditions cited above.

- **Pulmonary Arterial Hypertension:** The CHEST guideline and Expert Panel Report regarding therapy for PAH in adults (2019) details many medications. It was noted that PDE5 inhibitors play a vital role and have various benefits in the management of PAH.[10] The European Society of Cardiology and the European Respiratory Society guidelines regarding the treatment of pulmonary hypertension (2022) also recognize PDE5 inhibitors as having a prominent role in the management of this condition, as monotherapy or in use as combination with other agents.[11]

- **Systemic Sclerosis:** In 2017, the European League Against Rheumatism updated recommendations for the treatment of systemic sclerosis.[12] Dihydropyridine calcium channel blockers, usually oral nifedipine, are recommended for first-line therapy of Raynaud phenomenon in patients with systemic sclerosis. PDE5 inhibitors should be considered in such clinical scenarios as well.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Adcirca, Alyq, Liqrev, Revatio (tablets and suspension only), and Tadliq. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Adcirca, Alyq, Liqrev, Revatio (tablets and suspension only), and Tadliq, as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for initiation of therapy as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and catheterization laboratory reports. For a patient case in which the documentation requirement of the right heart catheterization upon Prior Authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this *Pulmonary Arterial Hypertension – Phosphodiesterase Type 5 Inhibitors Prior Authorization Policy* is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Adcirca, Alyq, Liqrev, Revatio, and Tadliq is recommended in those who meet the following criteria:

FDA-Approved Indication

25. Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1]. Approve for the duration noted if the patient meets ONE of the following (A or B):

G) Initial Therapy. Approve for 1 year if the patient meets all of the following (i and ii):

i. Patient meets the following (a and b):

a) Patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND

b) Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

ii. The medication is prescribed by or in consultation with a cardiologist or a pulmonologist.

H) Patient is Currently Receiving the Requested Phosphodiesterase Type 5 (PDE5) Inhibitor. Approve for 1 year if the patient meets the following (i and ii):

ix. Patient meets the following (a and b):

a) Patient has had a right heart catheterization; AND

b) Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

x. The medication is prescribed by or in consultation with a cardiologist or a pulmonologist.

Other Uses with Supportive Evidence

26. Raynaud's Phenomenon. Approve for 1 year if the patient meets ONE of the following (A or B):

A) Patient has tried one calcium channel blocker; OR
Note: Examples of calcium channel blockers include amlodipine, felodipine, and nifedipine.

B) According to the prescriber, use of a calcium channel blocker is contraindicated.
Note: Examples of reasons a patient cannot take calcium channel blocker therapy include right heart failure and decreased cardiac output.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Adcirca, Alyq, Liqrev, Revatio, and Tadliq is not recommended in the following situations:

3. Concurrent Use With Guanylate Cyclase Stimulators. Use of Adcirca, Alyq, Liqrev, Revatio, and/or Tadliq with guanylate cyclase stimulators is contraindicated.[13]
Note: An example of a guanylate cyclase stimulator is Adempas (riociguat tablets).

4. Erectile Dysfunction. Coverage is not recommended. Patients should use other phosphodiesterase type 5 (PDE5) inhibitors indicated for erectile dysfunction (i.e., Viagra [sildenafil tablets], Cialis [tadalafil tablets]).[14,15]

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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20. Adempas tablets® [prescribing information]. Whippany, NJ: Bayer; September 2021.
21. Viagra® tablets [prescribing information]. New York, NY: Pfizer; December 2017.
22. Cialis® tablets [prescribing information]. Indianapolis, IN: Eli Lilly; April 2023.
23. Liqrev® suspension [prescribing information]. Farmville, NC: CMP; April 2023.
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PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Treprostinil Injection Prior Authorization Policy
- Remodulin® (treprostinil subcutaneous or intravenous infusion – United Therapeutics, generic)

REVIEW DATE: 10/04/2023

OVERVIEW

Treprostinil injection, a prostacyclin vasodilator, is indicated for the treatment of pulmonary arterial hypertension (PAH) [World Health Organization {WHO} Group 1] to:[1,2]
- **Diminish symptoms associated** with exercise.
- **Reduce the rate of clinical deterioration** for patients who require transition from epoprostenol.

Treprostinil injection has been used with varying results in patients with chronic thromboembolic pulmonary hypertension (CTEPH).[3-7] Benefits noted include improvement in functional class, six-minute walk distance, and in hemodynamic parameters. Treprostinil injection is sometimes used as a bridge prior to surgery. Limited options are available for patients with CTEPH.

Disease Overview

PAH is a serious but rare condition impacting fewer than 20,000 patients in the US.[8,9] The estimated incidence of PAH is 2 cases per 1 million per year with a prevalence of 10.6 cases per 1 million adults.[8] It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized.[8,9] In this progressive disorder the small arteries in the lungs become narrowed, restricted, or blocked causing the heart to work harder to pump blood, leading to activity impairment. In time, right-sided heart failure and/or death may occur. Common PAH symptoms include shortness of breath, fatigue, chest pain, dizziness, and fainting, along with impairment in activity tolerance. It is more prevalent in women. Patients of all ages may develop the disease; however, the mean age of diagnosis typically happens between 36 to 50 years. Children may also have PAH. The condition may occur due to various underlying medical conditions or as a disease (e.g., connective tissue disease, HIV) that uniquely impacts the pulmonary circulation; both genetic and environmental factors may be involved. PAH is defined as a mean pulmonary artery pressure (mPAP) > 20 mmHg (at rest) with a pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg and a pulmonary vascular resistance > 2 Wood units measured by cardiac catheterization.[14] The prognosis in PAH has been described as poor, with the median survival being approximately 3 years. However, primarily due to advances in pharmacological therapies, the long-term prognosis has improved. Lung transplantation may be recommended if pharmacological or medical therapies fail, based upon patient status. The WHO categorizes PAH into stages, which is also referred to as the functional class (Class I to IV) and is an adaptation of the New York Heart Association system to evaluate activity tolerance.

CTEPH is a persistent obstruction of pulmonary arteries and is often a complication of pulmonary embolism.[10,11] It is classified within Group 4 pulmonary hypertension. Symptoms include progressive dyspnea on exertion, as well as fatigue, syncope, hemoptysis, and signs of right heart failure. Pulmonary endarterectomy is the treatment of choice for most patients with CTEPH. However, around 40% of patients are deemed inoperable for various reasons. Medication therapy may also be recommended. Anticoagulant therapy is also given.

Guidelines

Several guidelines address treprostinil injection in the management of pulmonary hypertension.[9,12]

- **Pulmonary Arterial Hypertension:** An updated CHEST guideline and Expert Panel Report regarding therapy for PAH in adults (2019) provides the evidence for use of the many medications for this condition.[9] In the absence of contraindications, patients with PAH should undergo acute vasoreactivity testing utilizing a short-acting agent (e.g., calcium channel blockers). For patients in Functional Class II, oral therapies are recommended such as endothelin receptor antagonists (ambrisentan, bosentan, Opsumit® [macitentan tablets]), phosphodiesterase type 5 inhibitors (tadalafil, sildenafil), and Adempas® (riociguat tablets). It is suggested that parenteral or inhaled prostanoids not be chosen as initial therapy for treatment naïve patients with PAH with WHO Functional Class II symptoms or as second-line agents for patients with PAH with WHO Functional Class II who have not met their treatment goals. Prostanoids may be considered in patients who have contraindications or difficulty tolerating phosphodiesterase type 5 inhibitors or endothelin receptor antagonists. Parenteral prostanoids are recommended for patients with PAH in Functional Class III and IV.[9] The European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines regarding the treatment of pulmonary hypertension (2022) also recognize parenteral treprostinil as having a prominent role in the management of this condition, usually in later therapy stages and after other therapies.[12]
- **Chronic Thromboembolic Pulmonary Hypertension:** Guidelines from the ESC/ERS regarding the treatment of pulmonary hypertension (2022) recommended to consider parenteral prostacyclin analogs for patients with inoperable CTEPH.[12]

Safety

Treprostinil injection should not be abruptly discontinued or have the dose rapidly decreased as rebound pulmonary hypertension may occur.[1,2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of treprostinil injection. All approvals are provided for 1 year in duration unless otherwise noted below. Specifically, approvals will remain up to 14 days for patients currently receiving the agent for the indication of PAH (WHO Group 1) with inadequate information or if the criteria are not met. These cases are reviewed by a nurse or pharmacist. Because of the specialized skills required for evaluation and diagnosis of patients treated with treprostinil injection as well as the monitoring required for adverse events and long-term efficacy, approval requires treprostinil injection to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: In the *Pulmonary Arterial Hypertension – Treprostinil Injection Prior Authorization Policy*, documentation is required for initiation of therapy where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and catheterization laboratory results. For a patient case in which the documentation requirement of the right heart catheterization upon Prior Authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this *Pulmonary Arterial Hypertension – Treprostinil Injection Prior Authorization Policy* is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of treprostinil injection is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. **Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1].** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets all of the following (i, ii, iii, iv, and v):
     - **i.** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
     - **ii.** Patient meets the following (a and b):
       - **a)** Patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND
       - **b)** Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
     - **iii.** Patient meets ONE of the following (a or b):
       - **a)** Patient is in Functional Class III or IV; OR
       - **b)** Patient is in Functional Class II and meets ONE of the following criteria [(1) or (2)]:
         - **(1)** Patient has tried or is currently receiving one oral agent for PAH; OR
           XX) Note: Examples of oral agents for PAH include bosentan, ambrisentan, Opsumit (macitentan tablets), Adempas (riociguat tablets), sildenafil, tadalafil, Alyq (tadalafil tablets), Tadliq (tadalafil oral suspension), Orenitram (treprostinil extended-release tablets) and Uptravi (selexipag tablets).
         - **(2)** Patient has tried one inhaled or parenteral prostacyclin product for PAH; AND
           YY) Note: Examples of inhaled and parenteral prostacyclin products for PAH include Ventavis (iloprost inhalation solution), Tyvaso (treprostinil inhalation solution), Tyvaso DPI (treprostinil oral inhalation powder), and epoprostenol intravenous infusion (Flolan, Veletri, generics).
     - **iv.** Patient with idiopathic PAH must meet ONE of the following (a, b, c, d, or e):
       - **a)** Patient meets both of the following criteria [(1) and (2)]:
         - According to the prescriber, the patient has had an acute response to vasodilator testing that occurred during the right heart catheterization; AND
           ZZ) Note: An example of a response can be defined as a decrease in mean pulmonary artery pressure of at least 10 mm Hg to an absolute mean pulmonary artery pressure of less than 40 mm Hg without a decrease in cardiac output.
         - Patient has tried one calcium channel blocker (CCB) therapy; OR
           AAA) Note: Examples of CCBs include amlodipine and nifedipine extended-release tablets.
       - **b)** According to the prescriber, the patient did not have an acute response to vasodilator testing; OR
       - **c)** According to the prescriber, the patient cannot undergo a vasodilator test; OR
       - **d)** Patient cannot take CCB therapy; OR

       BBB) Note: Examples of reasons a patient cannot take CCB therapy include right heart failure or decreased cardiac output.
       - **e)** Patient has tried one CCB; AND

       CCC) Note: Examples of CCBs include amlodipine and nifedipine extended-release tablets.
     - **v.** Medication is prescribed by or in consultation with a cardiologist or a pulmonologist; OR

B) Patient Currently Receiving Treprostinil Injection. Approve for the duration noted below if the patient meets ONE of the following (i or ii):

iii. Approve for 1 year if the patient meets ALL of the following (a , b, and c):

d) Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

e) Patient meets the following [(1) and (2)]:

(1) Patient has had a right heart catheterization; AND

(2) Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

f) Medication is prescribed by or in consultation with a cardiologist or a pulmonologist; OR

iv. Approve a short-term supply of treprostinil injection for up to 14 days if the patient does not meet the criteria in 1Bi above or if there is insufficient information available. All approvals are reviewed by a nurse or pharmacist.

Note: A 14-day supply should be sufficient to address coverage issues. However, multiple short-term approvals are allowed if a coverage determination cannot be made. Abrupt discontinuation of treprostinil injection therapy may have severe adverse consequences.

Other Uses with Supportive Evidence

2. Chronic Thromboembolic Pulmonary Hypertension (CTEPH). Approve for 1 year if prescribed by or in consultation with a pulmonologist or a cardiologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of treprostinil injection is not recommended in the following situations:

4. Chronic Obstructive Pulmonary Disease (COPD) in a Patient without PAH (WHO Group 1). COPD is classified as Group 3 Pulmonary Hypertension (pulmonary hypertension associated with lung diseases and/or hypoxia). Pulmonary hypertension may develop late in the course of COPD, but medications used for the treatment of PAH (WHO Group 1) are not recommended therapies.[13]

5. Concurrent Use with Parenteral Epoprostenol Products, Oral Prostacyclin Products, or Inhaled Prostacyclin Agents Used for Pulmonary Hypertension.
Note: Examples of medications include Orenitram (treprostinil extended-release tablets), Uptravi (selexipag tablets and intravenous infusion), Tyvaso (treprostinil inhalation solution), Tyvaso DPI (treprostinil oral inhalation powder), Ventavis (iloprost inhalation solution), and epoprostenol injection (Flolan, Veletri, generic).

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Uptravi Prior Authorization Policy
- Uptravi® (selexipag tablets – Actelion/Janssen)
  Note: Uptravi injection is not included in this policy

REVIEW DATE: 10/11/2023

OVERVIEW

Uptravi, a prostacyclin receptor agonist, is indicated for the treatment of **pulmonary arterial hypertension (PAH) World Health Organization (WHO) Group 1** to delay disease progression and reduce the risk of hospitalization for PAH.[1]

Disease Overview

PAH is a serious but rare condition impacting fewer than 20,000 patients in the US.[2,3] It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized. In this progressive disorder the small arteries in the lungs become narrowed, restricted, or blocked causing the heart to work harder to pump blood, leading to activity impairment. Although the mean age of diagnosis is between 36 and 50 years, patients of any age may be affected, including pediatric patients. PAH is defined as a mean pulmonary artery pressure (mPAP) > 20 mmHg (at rest) with a pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg and a pulmonary vascular resistance > 2 Wood units measured by cardiac catheterization.[5] The prognosis in PAH has been described as poor, with the median survival being approximately 3 years. However, primarily due to advances in pharmacological therapies, the long-term prognosis has improved.

Guidelines

Various guidelines address oral prostacyclin products.[3,4] The CHEST guideline and Expert Panel Report regarding therapy for pulmonary arterial hypertension (2019) in adults details many medications.[3] It was cited that many agents with varying mechanisms of action are used for the management of PAH. It was noted that the addition of an oral prostanoid product is recommended in patients with PAH who are in Functional Class III without evidence of rapid disease progression or a poor prognosis among those not willing or able to manage parenteral prostanoids. The European Society of Cardiology and the European Respiratory Society guidelines regarding the treatment of pulmonary hypertension (2022) also recognize Uptravi as having a role in therapy, mainly as an agent to be added onto other PAH therapies.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Uptravi (tablets). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Uptravi as well as the monitoring required for adverse events and long-term efficacy, approval requires Uptravi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for initiation of therapy where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and catheterization laboratory reports. For a patient case in which the documentation requirement of the right heart catheterization upon Prior Authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this *Pulmonary Arterial Hypertension – Uptravi Prior Authorization Policy* is considered to be met.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Uptravi is recommended in those who meet the following criteria:

FDA-Approved Indication

3. Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1]. Approve for the duration noted if the patient meets ONE of the following (A or B):

I) Initial Therapy. Approve for 1 year if the patient meets the following (i, ii, iii, and iv):

i. Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

ii. Patient meets the following (a and b):

a) Patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND

b) Results for the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

iii. Patient meets ONE the of following (a or b):

a) Patient has tried or is currently receiving at least one oral medication for PAH from one of the three following different categories (either alone or in combination) each for ≥ 60 days: one phosphodiesterase type 5 (PDE5) inhibitor, one endothelin receptor antagonist (ERA), or Adempas (riociguat tablets); OR

Note: Examples of phosphodiesterase type 5 inhibitors include sildenafil and tadalafil. Examples of endothelin receptor antagonists include bosentan, ambrisentan, and Opsumit (macitentan tablets).

b) Patient is currently receiving, or has a of receiving, one prostacyclin therapy for PAH; AND

Note: Examples of prostacyclin therapies for PAH include Orenitram (treprostinil tablets), Tyvaso (treprostinil inhalation solution), Tyvaso DPI (treprostinil inhalation solution), Ventavis (iloprost inhalation solution), treprostinil injection, and epoprostenol injection.

iv. The medication is prescribed by, or in consultation with, a cardiologist or a pulmonologist.

J) Patients Currently Receiving Uptravi. Approve for 1 year if the patient meets all of the following (i, ii, and iii):

i. Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

ii. Patient meets the following (a and b):

a) Patient has had a right heart catheterization; AND

b) Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

iii. The medication is prescribed by or in consultation with a cardiologist or a pulmonologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Uptravi is recommended in those who meet the following criteria:

72. Concurrent Use with Orenitram, Inhaled Prostacyclin Products, or Parenteral Prostacyclin Agents Used for Pulmonary Hypertension. Use in combination is not appropriate.
Note: Examples of medications include Tyvaso (treprostinil inhalation solution), Tyvaso DPI (treprostinil oral inhalation powder), Ventavis (iloprost inhalation solution), epoprostenol intravenous infusion, and treprostinil subcutaneous or intravenous infusion (Remodulin, generic).

73. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension and Related Lung Disease – Inhaled Prostacyclin Products Prior Authorization Policy
- Tyvaso® (treprostinil inhalation solution – United Therapeutics)
- Tyvaso DPI™ (treprostinil oral inhalation powder – MannKind/United Therapeutics)
- Ventavis® (iloprost inhalation solution – Actelion)

REVIEW DATE: 10/04/2023

OVERVIEW

Tyvaso, Tyvaso DPI, and Ventavis are inhaled prostacyclin vasodilators (prostacyclin mimetics) indicated for the treatment of:[1-3]

- **Pulmonary arterial hypertension (PAH), World Health Organization (WHO) Group 1**. Tyvaso and Tyvaso DPI are specifically indicated to improve exercise ability whereas Ventavis is indicated to improve a composite endpoint consisting of exercise tolerance, symptoms, and lack of deterioration.

Tyvaso and Tyvaso DPI are also indicated for:[1,2]

- **Pulmonary hypertension associated with interstitial lung disease (WHO Group 3)**. Tyvaso and Tyvaso DPI are indicated to improve exercise ability for this population.

Disease Overview

PAH is a serious but rare condition impacting fewer than 20,000 patients in the US.[4,5] It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized. In this progressive disorder, the small arteries in the lungs become narrowed, restricted, or blocked causing the heart to work harder to pump blood, leading to activity impairment. Although the mean age of diagnosis is between 36 and 50 years, patients of any age may be affected, including pediatric patients. PAH is defined as a mean pulmonary artery pressure (mPAP) > 20 mmHg (at rest) with a pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg and a pulmonary vascular resistance > 2 Wood units measured by cardiac catheterization.[11] The prognosis in PAH has been described as poor, with the median survival being approximately 3 years. However, primarily due to advances in pharmacological therapies, the long-term prognosis has improved.

Pulmonary hypertension due to interstitial lung disease (WHO Group 3) can complicate the condition and is associated with an increased need for supplemental oxygen, reduced mobility, and decreased survival.[7-10] Over 80% of patients with interstitial lung disease can have pulmonary hypertension; patients tend to be older and male.[6] Severe restrictions on pulmonary function tests and marked fibrosis on computed tomography scans are distinctions. The exact etiology is unknown. The symptoms are non-specific and include increased dyspnea on exertion, cough, fatigue, chest pain, and lower extremity edema. Tyvaso is the only medication indicated for this specific use. Randomized controlled trials utilizing other pulmonary vasodilators indicated for patients with WHO Group 1 PAH in patients with interstitial lung disease have not shown clear benefit and some studies suggest harm with use of some medications (e.g., sildenafil, Tracleer® [bosentan tablets], ambrisentan, Adempas® [riociguat tablets], and Opsumit® [macitentan tablets]).

Guidelines

Inhaled prostatcyclin products are included in various guidelines regarding PAH (WHO Group 1). Tyvaso DPI is not addressed yet.

- **Pulmonary Arterial Hypertension (PAH):** The CHEST guideline and Expert Panel Report regarding therapy for PAH (2019) in adults details many medications.[5] One recommendation is that parenteral or inhaled prostanoids should not be used as initial therapy for patients with PAH who are treatment naïve with WHO functional class II symptoms or as second-line agents for patients with PAH with WHO functional class II symptoms who have not met original treatment goals. In general, these agents are utilized in later stages of therapy.[5] The European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines regarding the treatment of pulmonary hypertension (2022) recognize that inhaled prostacyclin products have a role in therapy, mainly as an agent to be added onto other PAH therapies.[6]
- **Pulmonary Hypertension due to Interstitial Lung Disease:** The ESC/ERS guidelines regarding the treatment of pulmonary hypertension (2022) recommend inhaled treprostinil (Tyvaso) for patients with pulmonary hypertension associated with interstitial lung disease.[6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tyvaso, Tyvaso DPI, and Ventavis. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with these products as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for initiation of therapy as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and catheterization laboratory reports. For the use of PAH (WHO Group 1), for a patient case in which the documentation requirement of the right heart catheterization upon Prior Authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this *Pulmonary Arterial Hypertension and Related Lung Disease – Inhaled Prostacyclin Products Prior Authorization Policy* is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Tyvaso, Tyvaso DPI, and Ventavis is recommended in those who meet the following criteria:

FDA-Approved Indication

4. Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1]. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 year if the patient meets the following (i, ii, and iii):

i. Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

ii. Patient meets one of the following (a or b):

a) Patient is in Functional Class III or IV; OR

b) Patient is in Functional Class II and meets ONE of the following [(1) or (2)]:

(1) Patient has tried or is currently receiving one oral agent for PAH; OR
Note: Examples of oral agents for PAH include bosentan, ambrisentan, Opsumit (macitentan tablets), sildenafil, tadalafil, Adempas (riociguat tablets), Orenitram (treprostinil extended-release tablets), and Uptravi (selexipag tablets).

(2) Patient has tried one inhaled or parenteral prostacyclin product for PAH; AND
Note: Examples of inhaled and parenteral prostacyclin products for PAH include Tyvaso (treprostinil inhalation solution), Tyvaso DPI (treprostinil oral inhalation powder), Ventavis (iloprost inhalation solution), treprostinil injection, and epoprostenol injection.

iii. Patient meets the following (a and b):
- **a)** The patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND
- **b)** The results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

iv. The medication is prescribed by or in consultation with a cardiologist or a pulmonologist.

B) Patient is Currently Receiving the Requested Inhaled Prostacyclin. Approve for 1 year if the patient meets the following (i, ii, and iii):
- **i.** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
- **ii.** Patient meets the following (a and b):
  - **a)** Patient has had a right heart catheterization; AND
  - **b)** Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
- **iii.** The medication is prescribed by or in consultation with a cardiologist or a pulmonologist.

II. Coverage of Tyvaso and Tyvaso DPI is recommended in those who meet the following criteria:

FDA-Approved Indication

5. Pulmonary Hypertension Associated with Interstitial Lung Disease (World Health Organization [WHO] Group 3). Approve for the duration noted if the patient meets ONE of the following (A or B):
Note: This involves diagnosis such as idiopathic interstitial pneumonia, combined pulmonary fibrosis and emphysema, WHO Group 3 connective disease, and chronic hypersensitivity pneumonitis.

A) Initial Therapy. Approve for 4 months if the patient meets the following (i, ii, iii, iv, v, and vi):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has a diagnosis of World Health Organization (WHO) Group 3 pulmonary hypertension associated with interstitial lung disease; AND
- **iii.** Patient has connective tissue disease with a baseline forced vital capacity < 70%; AND
- **iv.** Patient has evidence of diffuse parenchymal lung disease on computed tomography of the chest; AND
- **v.** Patient meets the following (a and b):
  - **a)** Patient has had a right heart catheterization **[documentation required]**; AND
  - **b)** Results of the right heart catheterization confirm the diagnosis of WHO Group 3 pulmonary hypertension associated with interstitial lung disease; AND
- **vi.** The medication is prescribed by, or in consultation with, a cardiologist or a pulmonologist.

B) Patient is Currently Receiving Tyvaso or Tyvaso DPI for pulmonary hypertension associated with interstitial lung disease. Approve for 1 year if the patient meets the following (i, ii, iii, iv and v):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has a diagnosis of World Health Organization (WHO) Group 3 pulmonary hypertension associated with interstitial lung disease; AND
- **iii.** Patient meets the following (a and b):

a) Patient has had a right heart catheterization; AND
b) Results of the right heart catheterization confirm the diagnosis of World Health Organization (WHO) Group 3 pulmonary hypertension associated with interstitial lung disease; AND

iv. Patient has had a response to therapy according to the prescriber; AND
Note: Examples of a response include an increase or maintenance in the six-minute walk distance from baseline, improved exercise capacity, decrease in N-terminal pro-B-type natriuretic peptide levels, lessened clinical worsening, and a reduced rate of exacerbations of underlying lung disease.

v. The medication is prescribed by or in consultation with a cardiologist or a pulmonologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tyvaso, Tyvaso DPI, and Ventavis are not recommended in the following situations:

- **Concurrent Use with Oral or Parenteral Prostacyclin Agents Used for Pulmonary Hypertension.** Concomitant use is not recommended.
  Note: Examples of medications include Orenitram (treprostinil extended-release tablets), Uptravi (selexipag tablets and intravenous infusion), epoprostenol intravenous infusion, and treprostinil subcutaneous or intravenous infusion (Remodulin, generic).

- Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Qbrexza Prior Authorization Policy
- Qbrexza™ (glycopyrronium cloth 2.4% for topical use – Journey Medical)

REVIEW DATE: 12/06/2023

OVERVIEW

Qbrexza, an anticholinergic, is indicated for the topical treatment of **primary axillary** (i.e., underarm) **hyperhidrosis** in patients ≥ 9 years of age.[1] Qbrexza is applied topically once every 24 hours to clean dry skin on the underarm areas only; it is not for use on other body areas.

Guidelines

There are currently no guidelines for the treatment of hyperhidrosis published by a professional society. However, the International Hyperhidrosis Society, an independent, non-profit organization, provides an algorithm for the treatment of axillary hyperhidrosis (updated 2018).[2] Topical antiperspirant therapy or Qbrexza are both listed as initial treatment choices. It is noted in the algorithm that typically aluminum chloride hexahydrate 20% solution is the most commonly prescribed agent.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Qbrexza. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Qbrexza is recommended in those who meet the following criteria:

FDA-Approved Indication

i. Hyperhidrosis, Primary Axillary. Approve for 1 year if the patient meets the following (A, B, C, and D):
   a. Patient is ≥ 9 years of age; AND
   b. Hyperhidrosis is significantly interfering with the ability to perform age-appropriate activities of daily living; AND
   c. The prescriber has excluded secondary causes of hyperhidrosis; AND
   d. Patient meets one of the following (i or ii):
      i. Patient has tried one prescription aluminum chloride-containing topical antiperspirant for at least 4 weeks and experienced inadequate efficacy; OR
      ii. According to the prescriber, the patient has experienced significant intolerance with an aluminum-containing topical antiperspirant.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Qbrexza is not recommended in the following situations:

74. Hyperhidrosis, other than Primary Axillary. Qbrexza is not intended for application to areas other than the axillae.[1]

75. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Repository Corticotropin – Acthar Gel Prior Authorization Policy
- Acthar® Gel (repository corticotropin intramuscular and subcutaneous injection – Mallinckrodt)

REVIEW DATE: 04/19/2023

OVERVIEW

Acthar, an adrenocorticotropic hormone (ACTH) analog, is indicated for the following uses:[1]
- **Infantile spasms**, treatment of, in infants and children < 2 years of age.
- **Multiple sclerosis, treatment of exacerbations** in adults.

Although data are limited, the prescribing information notes that Acthar may also be used for the following disorders and diseases:[1]
- **Allergic states**, such as serum sickness.
- **Collagen diseases**, during an exacerbation or as a maintenance therapy in selected cases of systemic lupus erythematosus and systemic dermatomyositis (polymyositis).
- **Dermatologic diseases**, such as severe erythema multiforme and Stevens-Johnson syndrome.
- **Edematous state** including to induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus.
- **Respiratory diseases** such as symptomatic sarcoidosis.
- **Rheumatoid disorders**, as an adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in psoriatic arthritis, rheumatoid arthritis (including juvenile rheumatoid arthritis) [selected cases may require low-dose maintenance therapy], and ankylosing spondylitis.
- **Ophthalmic diseases** including severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, and anterior segment inflammation.

Clinical Efficacy

A review regarding repository corticotropin found few randomized controlled trials supporting the clinical benefit of repository corticotropin or ACTH for various conditions (e.g., use in rheumatoid arthritis, ankylosing spondylitis, optic neuritis, systemic lupus erythematosus, and nephrotic syndrome).[2] Most data suggest that repository corticotropin or ACTH was not superior to corticosteroids for treating relapses in patients with multiple sclerosis.

Guidelines

Several guidelines discuss repository corticotropin or ACTH.
- The **American Academy of Neurology and the Child Neurology Society** published an evidence-based guideline for the medical treatment of infantile spasms (2012).[3] ACTH is a first-line agent for the short-term treatment of infantile spasms.
- **Infantile Spasms Working Group** published a US consensus report on infantile spasms in 2010.[4] Most patients with this condition (90%) present within the first year of life. ACTH is an effective first-line therapy for infantile spasms.
- **Kidney Disease Improving Global Outcomes (KDIGO) published clinical practice guidelines for the management of glomerular disease (2021)**.[5] This includes diagnoses such as nephrotic syndrome, membranous nephropathy, immunoglobulin A nephropathy, minimal change disease, infection-related

glomerulonephritis, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, and lupus nephritis. ACTH is not prominent in the guidelines and there is a lack of quality evidence regarding ACTH.

- **National Multiple Sclerosis Society** has recommendations regarding corticosteroids in the management of multiple sclerosis relapses or exacerbations.[6] High-dose corticosteroids are the accepted standard of care short-term. The most common regimen is 500 to 1,000 mg of intravenous methylprednisolone given daily for 3 to 5 days, with or without an oral steroid tapering regimen (most often prednisone) for 1 to 3 weeks. ACTH and high-dose intravenous methylprednisolone have been shown to possess similar efficacy in the management of multiple sclerosis relapses.[7]
- The **American College of Rheumatology** has many guidelines regarding use in rheumatoid-type conditions.[8] ACTH does not have a prominent role and is generally not recommended for use in any of the related American College of Rheumatology guidelines.
- **The American College of Rheumatology has guidelines for the management of gout** (2020).[9] For gout flare management, using colchicine, non-steroidal anti-inflammatory drugs, or glucocorticoids (oral, intraarticular, or intramuscular) are appropriate first-line therapy for gout flare over interleukin-1 inhibitors or ACTH.
- **The European Respiratory Society published guidelines on the treatment of sarcoidosis (2021)**.[10] Repository corticotropin use should be reserved for patients who have failed prior treatments (e.g., steroids, antimetabolites). Only limited data are available. Repository corticotropin should be considered in a case by case basis only when other therapies are not effective or tolerated.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Acthar. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Acthar as well as monitoring required for adverse events and efficacy, approval requires Acthar to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Acthar is recommended in those who meet the following criteria:

FDA-Approved Indication

6. **Infantile Spasms, Treatment.** Approve Acthar for 1 month if the patient meets the following criteria (A and B):
   A) Child is < 2 years of age; AND
   B) Medication is prescribed by a physician who has consulted with or specializes in neurology.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Acthar is not recommended in the following situations:

76. Ankylosing Spondylitis. The American College of Rheumatology guidelines for the treatment of ankylosing spondylitis do not convey a role for ACTH in this condition.[11,12]

77. Dermatomyositis or Polymyositis. British Society for Rheumatology guidelines on the management of pediatric, adolescent, and adult patients with idiopathic inflammatory myopathy (2022) do not cite ACTH as an agent to utilize in patients with such conditions.[13]

78. Diabetic Nephropathy. ACTH is not a cited therapy or the standard of care for the management of chronic kidney disease in patients with diabetes.[5,14]

79. Glomerular Kidney Diseases.
Note: Diagnoses can include nephrotic syndrome, membranous nephropathy, immunoglobulin A nephropathy, minimal change disease, infection-related glomerulonephritis, focal segmental glomerulosclerosis, and membranoproliferative glomerulonephritis. ACTH is not prominent in related guidelines from KDIGO (2021) and there is a lack of quality evidence regarding ACTH to support its use.[5]

80. Gout. American College of Rheumatology guidelines for gout (2020) recommend other therapies beside ACTH for gout flare management (e.g., colchicine, non-steroidal anti-inflammatory drugs, or glucocorticoids).[9]

81. Juvenile Idiopathic Arthritis. Related guidelines from the American College of Rheumatology regarding the treatment of juvenile idiopathic arthritis (2021) do not mention ACTH as having a role for this disease.[15]

82. Lupus Nephritis. The KDIGO guidelines for the management of glomerular disease (2021) cite many other agents besides ACTH for the management of this condition.[5] The European League Against Rheumatism-European Renal Association-European Dialysis and Transplantation Association joint recommendations on the management of lupus nephritis do not cite ACTH as a therapy to use in this condition.[16]

83. Multiple Sclerosis, Acute Exacerbations. High-dose corticosteroids, usually intravenous methylprednisolone, are the accepted standard of care short-term for acute relapses or exacerbations.[6]

84. Ophthalmic Conditions. Only limited data describe the use of ACTH in ophthalmic-related conditions (e.g., acute optic neuritis, keratitis, retinal vasculitis).[2,17-19] Prospective data are needed to more rigorously define the efficacy and safety of ACTH in ocular disease.

85. Psoriatic Arthritis. The American College of Rheumatology/National Psoriasis Foundation guidelines for the treatment of psoriatic arthritis (2018) do not mention a role for ACTH in this condition.[20]

86. Rheumatoid Arthritis. The American College of Rheumatology guidelines for the treatment of rheumatoid arthritis (2021) do not mention a role for ACTH in this disease state.[21]

87. Sarcoidosis. The European Respiratory Society published guidelines on the treatment of sarcoidosis (2021).[10] Repository corticotropin use should be reserved for patients who have failed prior treatments

(e.g., steroids, antimetabolites). Only limited data are available. Repository corticotropin should be considered in a case by case basis only when other therapies are not effective or tolerated.

88. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Repository Corticotropin – Cortrophin Gel Prior Authorization Policy
- Purified Cortrophin™ Gel (repository corticotropin subcutaneous and intramuscular injection – ANI)

REVIEW DATE: 04/19/2023

OVERVIEW

Cortrophin Gel, a porcine derived purified corticotrophin (adrenocorticotropic hormone [ACTH] {1-39}) product, is indicated in the following disorders:[1]

- **Allergic states**, such as atopic dermatitis and serum sickness.
- **Collagen diseases**, during an exacerbation or as a maintenance therapy in selected cases of systemic lupus erythematosus and systemic dermatomyositis (polymyositis).
- **Dermatologic diseases**, such as severe erythema multiforme (Stevens-Johnson syndrome) and severe psoriasis.
- **Edematous state** including to induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus.
- **Nervous system**, acute exacerbations of multiple sclerosis.
- **Respiratory diseases** such as symptomatic sarcoidosis.
- **Rheumatoid disorders**, as an adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in psoriatic arthritis, rheumatoid arthritis (including juvenile rheumatoid arthritis) [selected cases may require low-dose maintenance therapy], ankylosing spondylitis, and acute gouty arthritis.
- **Ophthalmic diseases** including severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as allergic conjunctivitis, keratitis, iritis and iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, and anterior segment inflammation.

Clinical Efficacy

A recent review regarding repository corticotropin found few randomized controlled trials supporting the clinical benefit of repository corticotropin or ACTH for various conditions (e.g., use in rheumatoid arthritis, ankylosing spondylitis, optic neuritis, systemic lupus erythematosus, and nephrotic syndrome).[2] Most data suggest that repository corticotropin or ACTH was not superior to corticosteroids for treating relapses in patients with multiple sclerosis.

Guidelines

Several guidelines discuss repository corticotrophin or ACTH.

- **Kidney Disease Improving Global Outcomes (KDIGO) published clinical practice guidelines for the management of glomerular disease** (2021).[3] This includes diagnoses such as nephrotic syndrome, membranous nephropathy, immunoglobulin A nephropathy, minimal change disease, infection-related glomerulonephritis, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, and lupus nephritis. ACTH is not prominent in the guidelines and there is a lack of quality evidence regarding ACTH.
- **National Multiple Sclerosis Society** has recommendations regarding corticosteroids in the management of multiple sclerosis relapses or exacerbations.[4] High-dose corticosteroids are the accepted standard of care short-term. The most common regimen is 500 to 1,000 mg of intravenous methylprednisolone given daily for 3 to 5 days, with or without an oral steroid tapering regimen (most

often prednisone) for 1 to 3 weeks. ACTH and high-dose intravenous methylprednisolone have been shown to possess similar efficacy in the management of multiple sclerosis relapses.[5]

- The **American College of Rheumatology** has many guidelines regarding use in rheumatoid-type conditions.[6] ACTH does not have a prominent role and is generally not recommended for use in any of the related American College of Rheumatology guidelines.
- The **American College of Rheumatology has guidelines for the management of gout** (2020).[7] For gout flare management, using colchicine, non-steroidal anti-inflammatory drugs, or glucocorticoids (oral, intraarticular, or intramuscular) are appropriate first-line therapy for gout flare over interleukin-1 inhibitors or ACTH.
- **The European Respiratory Society published guidelines on the treatment of sarcoidosis (2021)**.[8] Repository corticotropin use should be reserved for patients who have failed prior treatments (e.g., steroids, antimetabolites). Only limited data are available. Repository corticotropin should be considered in a case by case basis only when other therapies are not effective or tolerated.

POLICY STATEMENT

Due to the lack of updated clinical efficacy data and potential safety concerns with long-term use, **approval is not recommended** for Cortrophin Gel. The current Cortrophin Gel efficacy information is insufficient to determine if the medication demonstrates any clinically meaningful benefits beyond those provided by other available therapies.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cortrophin Gel is not recommended in the following situations:

89. Ankylosing Spondylitis. The American College of Rheumatology guidelines for the treatment of ankylosing spondylitis do not convey a role for ACTH in this condition.[9,10]

90. Dermatomyositis or Polymyositis. British Society for Rheumatology guidelines on the management of pediatric, adolescent, and adult patients with idiopathic inflammatory myopathy (2022) do not cite ACTH as an agent to utilize in patients with such conditions.[11]

91. Diabetic Nephropathy. ACTH is not a cited therapy or the standard of care for the management of chronic kidney disease in patients with diabetes.[3,12]

92. Glomerular Kidney Diseases.
Note: Diagnoses can include nephrotic syndrome, membranous nephropathy, immunoglobulin A nephropathy, minimal change disease, infection-related glomerulonephritis, focal segmental glomerulosclerosis, and membranoproliferative glomerulonephritis. ACTH is not prominent in related guidelines from KDIGO (2021) and there is a lack of quality evidence regarding ACTH to supports its use.[3]

93. Gout. American College of Rheumatology guidelines for gout (2020) recommend other therapies beside ACTH for gout flare management (e.g., colchicine, non-steroidal anti-inflammatory drugs, or glucocorticoids).[7]

94. Infantile Spasms, Treatment. Purified Cortrophin Gel is not FDA-approved for this use.[1]

95. Juvenile Idiopathic Arthritis. Related guidelines from the American College of Rheumatology regarding the treatment of juvenile idiopathic arthritis (2021) do not mention ACTH as having a role for this disease.[13]

96. Lupus Nephritis. The KDIGO guidelines for the management of glomerular disease (2021) cite many other agents besides ACTH for the management of this condition.[3] The European League Against Rheumatism-European Renal Association-European Dialysis and Transplantation Association joint recommendations on the management of lupus nephritis do not cite ACTH as a therapy to use in this condition.[14]

97. Multiple Sclerosis, Acute Exacerbations. High-dose corticosteroids, usually intravenous methylprednisolone, are the accepted standard of care short-term for acute relapses or exacerbations.[4]

98. Ophthalmic Conditions. Only limited data describes the use of ACTH in ophthalmic-related conditions (e.g., acute optic neuritis, keratitis, retinal vasculitis).[2,15-17] Prospective data are needed to more rigorously define the efficacy and safety of ACTH in ocular disease.

99. Psoriatic Arthritis. The American College of Rheumatology/National Psoriasis Foundation guidelines for the treatment of psoriatic arthritis (2018) do not mention a role for ACTH in this condition.[18]

100. Rheumatoid Arthritis. The American College of Rheumatology guidelines for the treatment of rheumatoid arthritis (2021) do not mention a role for ACTH in this disease state.[19]

101. Sarcoidosis. The European Respiratory Society published guidelines on the treatment of sarcoidosis (2021).[8] Repository corticotropin use should be reserved for patients who have failed prior treatments (e.g., steroids, antimetabolites). Only limited data are available. Repository corticotropin should be considered in a case by case basis only when other therapies are not effective or tolerated.

102. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Rituximab Intravenous Products Prior Authorization Policy
- Riabni™ (rituximab-arrx intravenous infusion – Amgen)
- Rituxan® (rituximab intravenous infusion – Genentech)
- Ruxience® (rituximab-pvvr intravenous infusion – Pfizer)
- Truxima® (rituximab-abbs intravenous infusion – Celltrion/Teva)

REVIEW DATE: 08/16/2023

OVERVIEW

Rituximab products are CD20-directed cytolytic antibodies. All approved rituximab intravenous products are indicated for treatment of the following conditions:

- **Chronic lymphocytic leukemia** (CLL), in combination with fludarabine and cyclophosphamide (FC) for the treatment of patients with previously untreated and previously treated CD20-positive disease.
- **Granulomatosis with polyangiitis** (Wegener's granulomatosis) and **microscopic polyangiitis** in adults, in combination with glucocorticoids.
- **Non-Hodgkin lymphoma** (NHL), for the following uses:
  - previously untreated follicular, CD20-positive disease, in combination with first-line chemotherapy, and in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as a single-agent maintenance therapy.
  - for relapsed or refractory, low-grade or follicular, CD20-positive, B-cell disease.
  - for non-progressing (including stable disease) low-grade, CD20-positive, B-cell disease as a single agent after first-line cyclophosphamide/vincristine/prednisone (CVP) chemotherapy.
  - for previously untreated diffuse large B-cell, CD20-positive disease, in combination with cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) or other anthracycline-based chemotherapy regimens.
- **Rheumatoid arthritis**, in adult patients with moderately to severely active disease, in combination with methotrexate for patients who have had an inadequate response to one or more tumor necrosis factor inhibitors (TNFis).

In addition to the above indications, Rituxan intravenous is also indicated for treatment of the following conditions:

- **Granulomatosis with polyangiitis** (Wegener's granulomatosis) and **microscopic polyangiitis** in patients ≥ 2 years of age, in combination with glucocorticoids.
- **Pemphigus vulgaris**, for adults with moderate to severe disease.
- **B-cell lymphoma,** in patients ≥ 6 months of age with previously untreated, advanced stage, CD20-positive diffuse large B-cell lymphoma, Burkitt lymphoma, Burkitt-like lymphoma, or mature B-cell acute leukemia in combination with chemotherapy.

Riabni, Ruxience, and Truxima are approved as biosimilar to Rituxan intravenous, indicating no clinically meaningful differences in safety and effectiveness and the same mechanism of action, route of administration, dosage form, and strength as Rituxan intravenous. However, minor differences in clinically inactive components are allowed. At this time, the biosimilars have only demonstrated biosimilarity, not interchangeability.

Guidelines

The use of rituximab is supported in clinical guidelines in numerous situations, both as first-line therapy and in patients who are refractory or have relapsed following treatment with other therapies.[4-21]

- **Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis:** Guidelines from the American College of Rheumatology (ACR) [2021] list rituximab among the alternatives for induction or maintenance of remission. Various regimens are recommended with a typical maximum of 1,000 mg/infusion. For maintenance dosing, at least 4 months should separate doses. The optimal dose of rituximab for remission maintenance remains uncertain. Although scheduled maintenance is conditionally recommended over use of CD19+ B-cell counts and/or ANCA titers to guide retreatment, there are data to support both approaches.
- **Immune Thrombocytopenia (ITP):** Guidelines from the American Society of Hematology (ASH) for ITP (2019) mention rituximab as an alternative for children and adults with ITP who do not respond to first-line treatment, and for adults who are corticosteroid-dependent.[17]
- **Multiple Sclerosis (MS):** In June 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[18] Rituximab is listed among various options, involving different mechanisms of action and modes of administration, which have shown benefits in patients with MS. The American Academy of Neurology has practice guidelines regarding disease-modifying therapies for adults with MS.[19] The guidelines mention rituximab for use in MS.
- **Neuromyelitis Optica Spectrum Disorders:** A review article lists rituximab as an effective treatment for neuromyelitis optica.[20]
- Oncology indications covered in National Comprehensive Cancer Network (NCCN) guidelines:[6]
    - **Acute Lymphoblastic Leukemia (ALL):** Guidelines (version 2.2023 – July 28, 2023) list rituximab in multiple regimens for Philadelphia chromosome (Ph)-negative disease for patients with CD20-positive disease.[11] In those with Ph-positive disease, rituximab should be considered in addition to chemotherapy for those with CD20-positive disease, especially in those < 60 years of age.
    - **B-Cell Lymphomas:** In the guidelines (version 5.2023 – July 07, 2023), rituximab is included in multiple treatment regimens across the spectrum of disease.[8] Guidelines for pediatric aggressive mature B-cell lymphomas (version 1.2023 – April 04, 2023) include rituximab intravenous as a component of treatment regimens for induction therapy/initial treatment and as subsequent therapy for relapsed or refractory disease.[9] For primary cutaneous B-cell lymphomas (version 1.2023 – January 5, 2023), rituximab is a treatment option for patients with primary cutaneous B-cell lymphoma.[10]
    - **CLL/Small Lymphocytic Lymphoma:** Rituximab features prominently in the guidelines (version 3.2023 – June 12, 2023) and is included in multiple treatment regimens across the spectrum of disease.[7]
    - **Graft-Versus-Host Disease (GVHD):** The hematopoietic cell transplantation guidelines (version 1.2023 – March 31, 2023) list rituximab among the agents used for steroid-refractory chronic GVHD.[15]
    - **Hairy Cell Leukemia:** Guidelines (version 1.2023 – August 30, 2022) recommend rituximab as a component in a preferred primary regimen, and in multiple regimens for relapsed/refractory disease (including in patients with progressive disease after relapsed/refractory therapy).[12]
    - **Hodgkin Lymphoma:** Guidelines (version 2.2023 – November 8, 2022) recommend rituximab ± chemotherapy and/or radiation (depending on the clinical presentation) in the first-line setting for nodular lymphocyte-predominant disease.[13] Rituximab is also used for relapsed/refractory disease and for maintenance. Guidelines for pediatric disease (version 2.2023 – March 9, 2023) include rituximab in regimens for primary treatment of nodular lymphocyte-predominant disease.[25]

- **Primary Central Nervous System Lymphoma:** Guidelines for central nervous system cancers (version 1.2023 – March 24, 2023) recommend rituximab in multiple regimens for induction therapy and relapsed or refractory primary central nervous system lymphoma.[24]
- **Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma:** Guidelines (version 1.2023 – July 6, 2022) include rituximab in regimens across the spectrum of disease (primary therapy, previously treated disease, and maintenance).[14]

- **Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitors:** NCCN (version 2.2023 – May 9, 2023) and the American Society of Clinical Oncology (ASCO) guidelines (2021) recommend rituximab as an option for corticosteroid-refractory dermatologic and hematologic immune mediated adverse events, as well as for immune-mediated encephalitis and myositis.[26,27]
- **Pemphigus Vulgaris:** British guidelines (2017) list rituximab in combination with corticosteroids as a first-line therapy.[23]
- **Rheumatoid Arthritis:** Guidelines from ACR (2021) recommend addition of a biologic or a targeted synthetic DMARD for a patient taking the maximum tolerated dose of methotrexate who is not at target.[16]
- **Systemic Lupus Erythematosus (SLE):** European League Against Rheumatism (EULAR) recommendations for the management of SLE (2019) mention rituximab as a therapeutic option for patients who are refractory to standard immunosuppressive therapies.[21]

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POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of rituximab intravenous products. Because of the specialized skills required for evaluation and diagnosis of patients treated with rituximab as well as the monitoring required for adverse events and long-term efficacy, initial approval requires rituximab intravenous products to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration listed below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of rituximab intravenous products is recommended in those who meet one of the following criteria:

FDA-Approved Indications

3. **Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Induction Treatment. Approve for 1 month if the patient meets ALL of the following (i, ii, and iii):
   - **i.** Patient has an ANCA-associated vasculotide; AND
     Note: Examples of ANCA-associated vasculitis include granulomatosis with polyangiitis (GPA) [Wegener's granulomatosis] or microscopic polyangiitis (MPA).
   - **ii.** The medication is being administered in combination with glucocorticoids; AND
   - **iii.** The medication is prescribed by or in consultation with a rheumatologist, nephrologist, or immunologist.
   - **B)** Follow-Up Treatment of Patients Who Have Received Induction Treatment for ANCA-Associated Vasculitis. Approve for 1 year if the patient meets BOTH of the following (i and ii):

Note: This includes a patient who received induction treatment using a rituximab product or other standard of care immunosuppressants.

i. According to the prescriber, the patient achieved disease control with induction treatment; AND

ii. If the patient previously received a course of therapy, at least 16 weeks will elapse between courses.

4. B-Cell Lymphoma. Approve for 1 year if prescribed by or in consultation with an oncologist.
Note: Examples of B-cell lymphomas include follicular lymphoma, diffuse large B-cell lymphoma, high-grade B-cell lymphoma, acquired immune deficiency (AIDS)-related B-cell lymphoma, Burkitt lymphoma, Castleman's disease, marginal zone lymphoma (e.g., extranodal or MALT [gastric or nongastric], nodal, or splenic marginal zone lymphoma), primary mediastinal large B-cell lymphoma, mantle cell lymphoma, post-transplant lymphoproliferative disorders, gray zone lymphoma, primary cutaneous B-cell lymphoma, pediatric aggressive mature B-cell lymphomas.

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5. Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. Approve for 1 year if prescribed by or in consultation with an oncologist.

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6. Pemphigus Vulgaris. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Treatment. Approve for 1 month (which is adequate duration to administer one course of therapy) if the patient meets BOTH of the following (i and ii):

i. Therapy is initiated in combination with a corticosteroid unless contraindicated; AND
Note: An example of a corticosteroid is prednisone.

ii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Being Treated for a Relapse or for Maintenance of Pemphigus Vulgaris. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Subsequent infusions will be administered no sooner than 16 weeks following the previous infusion of a rituximab product; AND

ii. The medication is prescribed by or in consultation with a dermatologist.

7. Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month (which is adequate duration to administer one course of therapy) if the patient meets ALL of the following conditions (i, ii, and iii):

i. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND
Note: Examples of conventional synthetic DMARDs include methotrexate [oral or injectable], leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient already has a 3-month trial of at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix A for examples of biologics used for rheumatoid arthritis. A patient who has already tried a biologic is not required to "step back" and try a conventional synthetic DMARD.

ii. The medication will not be used concurrently with another biologic or with a targeted synthetic DMARD; AND
Note: Refer to Appendix A for examples of biologics and targeted synthetic DMARDs.

iii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient has already Received One or More Courses of a Rituximab Product for Rheumatoid Arthritis. Approve for 1 month (which is adequate duration to administer one course of therapy) if the patient meets ALL of the following conditions (i, ii, and iii):

i. 16 weeks or greater will elapse between treatment courses; AND
Note: For example, there will be a minimum of 16 weeks since the first dose of the previous course and the first dose of the next course of a rituximab product.

ii. The medication will not be used concurrently with another biologic or with a targeted synthetic DMARD; AND
Note: Refer to Appendix A for examples of biologics and targeted synthetic DMARDs.

iii. If the patient has already received two or more courses of therapy, the patient meets at least ONE of the following (a or b):

a) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
Note: Examples of standardized and validated measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).

b) Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

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Other Uses with Supportive Evidence

6. Acute Lymphoblastic Leukemia. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient has CD20-positive disease; AND

B) The medication is prescribed by or in consultation with an oncologist.

7. Graft-Versus-Host Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month if the patient meets the following (i and ii):

i. Patient has tried at least one conventional systemic treatment for graft versus host disease; AND
Note: Examples include systemic corticosteroids (methylprednisolone, prednisone), cyclosporine, tacrolimus, mycophenolate mofetil, Imbruvica (ibrutinib capsules and tablets), imatinib, antithymocyte globulin, Nipent (pentostatin infusion), or an infliximab product.

ii. The medication is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center.

B) Patient has Already Received a Course of a Rituximab Product for Graft-Versus-Host Disease. Approve for 1 year if the patient meets at least ONE of the following (i or ii):

i. When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating a rituximab product); OR
Note: An example of objective measures is normalization of liver function tests, red blood cell count, or platelet count, or resolution of fever or rash.

ii. Compared with baseline (prior to initiating a rituximab product), patient experienced an improvement in at least one symptom, such as improvement in skin, oral mucosal, ocular, or gastrointestinal symptoms (e.g., nausea, vomiting, anorexia).

8. **Hairy Cell Leukemia.** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

9. **Hodgkin Lymphoma**. Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient has nodular lymphocyte-predominant disease; AND
   B) The medication is prescribed by or in consultation with an oncologist.

10. **Immune Thrombocytopenia (ITP).** Approve if the patient meets ONE of the following (A or B):
   A) Initial Therapy. Approve for 1 month if the patient meets BOTH of the following (i and ii):
   i. Patient has tried one other therapy; AND
   Note: Examples of therapies for ITP include intravenous immunoglobulin (IVIG), anti-D (RHO) immunoglobulin, corticosteroids, and splenectomy.
   ii. The agent is prescribed by or in consultation with a hematologist.
   B) Patient has Already Received a Course of a Rituximab Product for ITP. Approve for 1 month if the patient meets ALL of the following (i, ii, and iii):
   i. At least 6 months will elapse between treatment courses; AND
   Note: For example, there will be a minimum of 6 months separating the first dose of the previous course and the first dose of the requested course of a rituximab product.
   ii. Patient responded to therapy as determined by the prescriber; AND
   Note: Examples of a response include a platelet count increase from baseline following treatment with a rituximab product.
   iii. The prescriber has determined that the patient has relapsed.
   Note: Examples of a relapse include the patient experiences thrombocytopenia after achievement of a remission.

11. **Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitors.** Approve for the duration noted if the patient meets the following (A or B):
   Note: Examples of checkpoint inhibitors are Keytruda (pembrolizumab intravenous infusion), Opdivo (nivolumab intravenous infusion), Yervoy (ipilimumab intravenous infusion), Tecentriq (atezolizumab intravenous infusion), Bavencio (avelumab intravenous infusion), Imfinzi (durvalumab intravenous infusion), and Libtayo (cemiplimab-rwlc intravenous infusion).
   12. Initial Therapy. Approve for 1 month if the patient meets BOTH of the following (i and ii):
   i. Patient is symptomatic despite a trial of at least ONE systemic corticosteroid; AND
   Note: Examples of a corticosteroid include methylprednisolone and prednisone.
   ii. The medication is prescribed by or in consultation with an oncologist, neurologist, rheumatologist, or dermatologist.
   13. Patient has Already Received a Course of a Rituximab Product. Approve for 1 month if prescribed by or in consultation with an oncologist, neurologist, rheumatologist, or dermatologist.

14. **Multiple Sclerosis.** Approve for 1 year if the patient meets ONE of the following (A or B):
   A) Initial Therapy. Approve if the patient meets ALL the following (i, ii, iii, and iv):
   i. According to the prescriber, the patient has experienced inadequate efficacy or significant intolerance to at least TWO other disease-modifying agents for multiple sclerosis; AND
   Note: See Appendix B for examples of disease-modifying agents used for multiple sclerosis.
   ii. Medication will not be used concurrently with another disease-modifying agent used for multiple sclerosis; AND
   Note: See Appendix B for examples of disease-modifying agents used for multiple sclerosis.
   iii. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; AND

iv. At least 6 months will elapse between treatment courses.
Note: For example, if the patient has already received a course of therapy there will be a minimum of 6 months separating the first dose of the previous course and the first dose of the requested course of therapy.

B) Patient is Currently Receiving Rituximab. Approve if the patient meets one of the following (i or ii):

i. Patient has been receiving Rituximab for < 1 year. Approve if the patient meets ALL of the following (a, b, and c):

1. Medication will not be used concurrently with another disease-modifying agent used for multiple sclerosis; AND
   Note: See Appendix B for examples of disease-modifying agents used for multiple sclerosis.
2. At least 6 months will elapse between treatment courses; AND
   Note: For example, if the patient has already received a course of therapy there will be a minimum of 6 months separating the first dose of the previous course and the first dose of the requested course of therapy.
3. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR

ii. Patient has been receiving Rituximab for 1 year or more. Approve for 1 year if the patient meets ALL of the following (a, b, c, and d):

a) Medication will not be used concurrently with another disease-modifying agent used for multiple sclerosis; AND
Note: See Appendix B for examples of disease-modifying agents used for multiple sclerosis.

b) At least 6 months will elapse between treatment courses; AND
Note: For example, if the patient has already received a course of therapy there will be a minimum of 6 months separating the first dose of the previous course and the first dose of the requested course of therapy.

c) Patient meets ONE of the following [(1) or (2)]:

a. Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
   Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability Status Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Items Multiple Sclerosis Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and or attenuation of brain volume loss; OR
b. Patient experienced stabilization, slow progression, or improvement in at least one symptoms such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND

d) Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

13. Neuromyelitis Optica Spectrum Disorder. Approve for 1 month if prescribed by or in consultation with a neurologist.

14. **Primary Central Nervous System Lymphoma**. Approve for 1 year if prescribed by or in consultation with an oncologist.

15. **Systemic Lupus Erythematosus (SLE) [Lupus].** Approve for the duration noted if the patient meets ONE of the following (A or B):
    Note: This includes nephrotic syndrome in a patient with SLE.
    A) Initial Therapy. Approve for 1 month (adequate duration to receive one course) if the patient meets BOTH of the following (i and ii):
        i. Patient has tried at least ONE standard immunomodulating or immunosuppressant agent; AND
        Note: Examples of standard immunomodulating or immunosuppressant agents include hydroxychloroquine, corticosteroids (e.g., prednisone, methylprednisolone), methotrexate, azathioprine, mycophenolate, and cyclophosphamide.
        ii. The medication is prescribed by or in consultation with a rheumatologist, nephrologist, or neurologist.
    B) Patient has Already Received a Course of a Rituximab Product for SLE. Approve for 1 month (adequate duration to receive one course) if 6 months or greater will elapse between treatment courses
    Note: There will be a minimum of 6 months separating the first dose of the previous rituximab course and the first dose of the requested course of rituximab.

16. **Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma.** Approve for 1 year if prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of rituximab intravenous products is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX A

[*] Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; [^] Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis.

APPENDIX B

PRIOR AUTHORIZATION POLICY

POLICY: Scenesse Prior Authorization Policy
- Scenesse® (afamelanotide subcutaneous implant – Clinuvel)

REVIEW DATE: 01/11/2023

OVERVIEW

Scenesse, a melanocortin 1 receptor agonist, is indicated to increase pain-free light exposure in adults with a history of phototoxic reactions from **erythropoietic protoporphyria (EPP)**.[1] Scenesse is a controlled-release dosage form that is implanted subcutaneously (SC). Scenesse should be administered by a healthcare professional. A single implant which contains 16 mg of afamelanotide is inserted SC above the anterior supra-iliac crest once every 2 months.

Disease Overview

Porphyrias are disorders caused by enzyme defects in heme biosynthesis.[2] There are at least eight different types of porphyrias, which are classified as cutaneous or acute depending on the specific enzyme that is deficient. EPP is a cutaneous porphyria characterized by extreme photosensitivity. It is estimated to occur in 2 to 5 in 1,000,000 individuals.[3]

EPP occurs due to excessive accumulation of protoporphyrin, a heme precursor. Classic EPP is autosomal recessive and occurs due to a defect in the enzyme ferrochelatase, the final enzymatic step in heme biosynthesis.[4] An X-linked subtype of EPP, often referred as X-linked protoporphyria (XLP), accounts for 2% to 10% of all EPP cases. This type develops due to a gain-of-function mutation in an upstream enzyme in heme biosynthesis, leading to excess protoporphyrin production.[3,4] The two subtypes share the same biochemical and clinical features, although females with XLP may be less severely affected. Diagnosis is confirmed by one or both of the following: 1) biochemically via markedly elevated free erythrocyte protoporphyrin, and/or 2) molecular genetic testing.[2,3]

In both EPP subtypes, protoporphyrin accumulation in superficial skin vessels leads to phototoxicity upon light exposure, resulting in the hallmark symptoms of burning, tingling, and itching, which often occur without visible damage.[2-4] Phototoxic pain is not responsive to analgesics, including narcotics; management is focused on prevention of phototoxic episodes.[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Scenesse. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Scenesse as well as the monitoring required for adverse events and long-term efficacy, approval requires Scenesse to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Scenesse is recommended in those who meet the following criteria:

FDA-Approved Indication

8. Erythropoietic Protoporphyria (Including X-Linked Protoporphyria). Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has a of at least one porphyric phototoxic reaction; AND
- **C)** The diagnosis is confirmed by at least one of the following (i or ii):
  - **i.** Free erythrocyte protoporphyrin level above the normal reference range for the reporting laboratory; OR
  - **ii.** Molecular genetic testing consistent with the diagnosis; AND
- **D)** The agent is prescribed by or in consultation with a dermatologist, gastroenterologist, hepatologist, or physician specializing in the treatment of cutaneous porphyrias.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Scenesse is not recommended in the following situations:

69. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Sedative Hypnotics Medications Prior Authorization Policy for the InMynd Program

- Ambien® (zolpidem tablets – Sanofi-Aventis, generic)
- Ambien CR® (zolpidem extended-release tablets – Sanofi-Aventis, generic)
- Belsomra® (suvorexant tablets – Merck)
- Dayvigo® (lemborexant tablets – Eisai)
- Doral® (quazepam tablets – Galt)
- Edluar® (zolpidem sublingual tablets – Meda)
- estazolam tablets – generic only
- flurazepam capsules – generic only
- Halcion® (triazolam tablets – Pfizer, generic)
- Intermezzo® (zolpidem sublingual tablets – Purdue, generic)
- Lunesta® (eszopiclone tablets – Sunovion, generic)
- Quviviq® (daridorexant tablets – Idorsia)
- Rozerem® (ramelteon tablets – Takeda, generic)
- Restoril® (temazepam capsules – Mallinckrodt, generic)
- Silenor® (doxepin tablets – Somaxon, generic)
- Sonata® (zaleplon capsules – Pfizer, generic)
- Zolpimist® (zolpidem oral spray –Aytu BioScience)

REVIEW DATE: 06/07/2023; selected revision 07/12/2023

OVERVIEW

All of the medications included in this policy are indicated for the **treatment of insomnia**.[1-12]

Zolpidem immediate-release (IR) and extended-release (ER), Edluar, Zolpimist, zaleplon, and the benzodiazepine sedative hypnotics are indicated for the short-term treatment of insomnia.[1-3,5,6,12] Eszopiclone, Silenor, and Rozerem are also indicated for the treatment of insomnia, but their product labeling does not specifically limit their use to short-term.[4,8,9] All of the agents in this category have been shown to decrease sleep latency. Zaleplon and Rozerem are specifically indicated for the treatment of insomnia characterized by difficulty with sleep onset.[3,8] Zolpidem IR, zolpidem ER, Silenor, and eszopiclone have also been shown to improve sleep maintenance or increase the duration of sleep.[1,2,4,9] Belsomra, Dayvigo, and Quviviq are indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance.[10-12] Zolpidem sublingual tablets are indicated for use as needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep.[7]

Eszopiclone, zaleplon, zolpidem IR, zolpidem ER, zolpidem sublingual tablets, Edluar, Zolpimist, and the benzodiazepine sedative hypnotics are all schedule IV controlled substances.[1-7,12] Belsomra, Dayvigo, and Quviviq are also schedule IV controlled substances.[10-12] Neither Rozerem nor Silenor are controlled substances.[8,9] Doxepin is also available generically as oral capsules (10 mg, 25 mg, 50 mg, 75 mg, 100 mg, and 150 mg) and oral solution (10 mg/mL).[13] These higher dose formulations are recommended for use in patients with depression and/or anxiety of varying etiologies.

Disease Overview

Insomnia is defined in the International Classification of Sleep Disorders, Third Edition, as a complaint of trouble initiating or maintaining sleep, resulting in daytime consequences (e.g., daytime fatigue, irritability, and decreased concentration) which is not attributable to environmental circumstances or inadequate opportunity for sleep.[14] Generally, transient insomnia lasts less than 1 week, short-term (acute) insomnia lasts up to 3 months, and chronic insomnia lasts more than 3 months at a frequency of at least three times per week.[14,15] Describing insomnia by timing (difficulty falling asleep [sleep onset insomnia], difficulty staying asleep or getting back to sleep after awakening [sleep maintenance insomnia], or disrupted or non-refreshing sleep and/or early morning awakening) can be useful in the diagnosis and help to distinguish among sleep disorders. Additionally, the pattern of sleep difficulty provides a basis to match a medication based on timing of onset and duration of effect.

Guidelines

The American Academy of Sleep Medicine (AASM) published a clinical guideline for the evaluation and management of chronic insomnia in adults (2008).[17] The primary treatment goals are to improve sleep quality and quantity and to improve insomnia-related daytime impairments. Initial approaches to treatment should include at least one behavioral intervention such as stimulus control therapy or relaxation therapy, or the combination of cognitive therapy, stimulus control therapy, sleep restriction therapy with or without relaxation therapy. Patients should be instructed to keep a regular schedule; have a healthy diet, regular daytime exercise, and a quiet sleep environment; and avoid napping, caffeine, other stimulants, nicotine, alcohol, excessive fluids, or stimulating activities before bedtime. Short-term hypnotic treatment should be supplemented with behavioral and cognitive therapies when possible. Chronic hypnotic medication may be indicated for long-term use in patients with severe or refractory insomnia or chronic comorbid illness. Whenever possible, patients should receive an adequate trial of cognitive behavioral treatment during long-term pharmacotherapy. Long-term prescribing should be accompanied by regular follow-up, ongoing assessment of effectiveness, monitoring for adverse events, and evaluation for new onset or exacerbation of existing comorbid disorders.

The AASM published an updated clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults (2017).[14] The recommendations are intended as a guide for choosing a specific pharmacological agent (vs. no treatment) for treatment of chronic insomnia in adults, when such treatment is indicated. Each of the recommendations listed is weak, meaning it reflects a lower degree of certainty in the outcome and appropriateness of the patient care strategy for all patients but should not be construed as an indication of ineffectiveness. The guideline suggests that clinicians can use Belsomra as a treatment for sleep maintenance insomnia; eszopiclone can be used as a treatment for sleep onset and sleep maintenance insomnia; zaleplon can be used as a treatment for sleep onset insomnia; zolpidem can be used as a treatment for sleep onset and sleep maintenance insomnia; triazolam can be used as a treatment for sleep onset insomnia; temazepam can be used as a treatment for sleep onset and sleep maintenance insomnia; ramelteon can be used as a treatment for sleep onset insomnia; and Silenor can be used as a treatment for sleep maintenance insomnia. The guideline suggested that clinicians not use trazodone, tiagabine, diphenhydramine, melatonin, tryptophan, or valerian as a treatment for sleep onset or sleep maintenance insomnia. The authors note that cognitive behavioral therapy for insomnia (CBT-I) is a standard of care for this condition; however, the AASM guideline does not address the relative benefits of CBT-I vs. pharmacotherapy.

The American College of Physicians (ACP) developed a guideline on the management of chronic insomnia disorder in adults (2016).[18,19] The guideline is consistent with the AASM guidelines on chronic insomnia. Psychological therapy options include CBT-I and other interventions, such as stimulus control, relaxation strategies, and sleep restriction. ACP recommends that all adults receive CBT-I as the initial treatment for chronic insomnia disorder (strong recommendation, moderate-quality evidence). ACP recommends that

clinicians use a shared decision-making approach, including a discussion of the benefits, harms, and costs of short-term use of medications, to decide whether to prescribe a medication in adults with chronic insomnia disorder in whom CBT-I alone was unsuccessful (weak recommendation, low-quality evidence). A review of the evidence found that eszopiclone, zolpidem, Belsomra, and Silenor may improve short-term global and sleep outcomes for adults with insomnia disorder (low- to moderate-quality evidence), but the comparative effectiveness and long-term efficacy of pharmacotherapies for insomnia are unknown.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of sedative hypnotics. All approvals are provided for the duration noted below.

Automation: A patient who uses at least 180 days of any sedative/hypnotic medication in a 365-day time period will require Prior Authorization. If the patient has a prescription for a cancer medication (see Appendix A) within a 180-day period, the claim will adjudicate. If a patient has received at least 300 days of a sedative/hypnotic medication in a 545-day time period, the claim will adjudicate. When available, the ICD-10 codes for cancer will be used as part of automation to allow approval of the requested medication (see Appendix B).

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of a sedative hypnotic is recommended in those who meet the following criteria:

FDA-Approved Indication

F) Chronic Insomnia. Approve for 1 year if the patient meets ONE of the following (A or B):

E) Patient has a cancer diagnosis; OR

F) Patient meets ALL of the following (i, ii, iii, and iv):

- **i)** Patient has tried at least one form of behavioral therapy for insomnia; AND
  Note: Examples of behavioral therapy for insomnia include relaxation training, stimulus control therapy, or sleep restriction therapy.
- **ii)** Patient is not currently taking prescription stimulants (e.g., methylphenidate, amphetamine products); AND
- **iii)** Underlying psychiatric and/or medical conditions that may cause or exacerbate insomnia have been evaluated and are currently being addressed, according to the prescriber; AND
- **iv)** Patient's sleep quality and quantity and/or insomnia-related daytime impairments continue to improve or remain stable while on a sedative hypnotic agent, according to the prescriber.
  Note: Prior Authorization is required after 6 months of use of any (or any combination of) sedative-hypnotic agent(s) [not necessarily 6 months of the drug being requested].

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of sedative hypnotics is not recommended in the following situations:

70. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX A

Note: This list is not inclusive. As new STCs become available, they will roll into this policy and the list will be updated periodically.

* Excluding topical products.

APPENDIX B

*Indicates the inclusion of subheadings.

PRIOR AUTHORIZATION POLICY

POLICY: Sickle Cell Disease – Adakveo Prior Authorization Policy
- Adakveo® (crizanlizumab-tmca intravenous infusion – Novartis)

REVIEW DATE: 12/07/2022

OVERVIEW

Adakveo, a monoclonal antibody, is indicated to **reduce the frequency of vasoocclusive crises** in patients 16 years and older with **sickle cell disease**.[1]

Guidelines

The American Society of Hematology guidelines for sickle cell disease: management of acute and chronic pain associated with sickle cell disease (2020) does not address the use of Adakveo.[2] The National Institutes of Health – National Heart, Lung, and Blood Institute issued the Evidence-Based Management of Sickle Cell Disease, Expert Panel Report in 2014.[3] These guidelines were published prior to the approval of Adakveo. Hydroxyurea has been shown to reduce the frequency of painful episodes, the incidence of acute coronary syndrome events, and the need for transfusions and hospitalizations.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Adakveo. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Adakveo as well as the monitoring required for adverse events and long-term efficacy, approval requires Adakveo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Adakveo is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Sickle Cell Disease.** Approve for 1 year if the patient meets ONE of the following criteria (A or B):
   - **A)** Initial Therapy. Approve if the patient meets ALL of the following criteria (i, ii, iii, and iv):
     - **i.** Patient is ≥ 16 years of age; AND
     - **ii.** Patient has had at least one sickle-cell related crisis in the previous 12-month period; AND
     - **iii.** Patient meets one of the following criteria (a, b, or c):
       - **a)** Patient is currently receiving a hydroxyurea product; OR
       - **b)** According to the prescriber, patient has tried a hydroxyurea product and has experienced inadequate efficacy or significant intolerance; OR
       - **c)** According to the prescriber, patient is not a candidate for hydroxyurea therapy; AND
         Note: Examples of patients who are not candidates for hydroxyurea therapy include patients who are pregnant or who are planning to become pregnant and patients with an immunosuppressive condition (such as cancer).

iv. The medication is prescribed by or in consultation with a physician who specializes in sickle cell disease (e.g., a hematologist).

B) Patient is Currently Receiving Adakveo. Approve if the patient meets ALL of the following criteria (i, ii, and iii):

15. Patient is ≥ 16 years of age; AND

16. According to the prescriber, patient is receiving clinical benefit from Adakveo therapy; AND
Note: Examples of clinical benefit include reduction in the number of vasoocclusive crises/sickle cell-related crises; delay in time to sickle cell-related crises; and reduction in the number of days in the hospital.

17. The medication is prescribed by or in consultation with a physician who specializes in sickle cell disease (e.g., a hematologist).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Adakveo is not recommended in the following situations:

71. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Sickle Cell Disease – Endari Prior Authorization Policy
- Endari™ (L-glutamine oral powder – Emmaus Medical)

REVIEW DATE: 12/07/2022

OVERVIEW

Endari is indicated to **reduce the acute complications of sickle cell disease** in patients ≥ 5 years of age.[1]

L-GLUTAMINE IS AN ESSENTIAL AMINO ACID AND SERVES AS A PRECURSOR OF NUCLEIC ACIDS AND NUCLEOTIDES INCLUDING THE PYRIDINE NUCLEOTIDES (NICOTINAMIDE ADENINE DINUCLEOTIDE AND REDUCED NICOTINAMIDE ADENINE DINUCLEOTIDE).[1,2] THESE PYRIDINE NUCLEOTIDES PLAY KEY ROLES IN THE REGULATION AND PREVENTION OF OXIDATIVE DAMAGE IN RED BLOOD CELLS AND STUDIES HAVE SHOWN THAT OXIDATIVE PHENOMENA MAY PLAY A SIGNIFICANT ROLE IN THE PATHOPHYSIOLOGY OF SICKLE CELL DISEASE.

Guidelines

The American Society of Hematology guidelines for sickle cell disease: management of acute and chronic pain associated with sickle cell disease (2020) does not mention the use of L-glutamine.[2] The National Institutes of Health – National Heart, Lung, and Blood Institute issued the Evidence-Based Management of Sickle Cell Disease, Expert Panel Report in 2014.[3] The use of L-glutamine products in sickle cell disease is not mentioned (guidelines were published before the approval of Endari). Hydroxyurea has been shown to reduce the frequency of painful episodes, the incidence of acute coronary syndrome events, and the need for transfusions and hospitalizations.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Endari. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Endari as well as the monitoring required for adverse events and long-term efficacy, approval requires Endari to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Endari as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Endari is recommended in those who meet the following criteria:

FDA-Approved Indication

18. Sickle Cell Disease [documentation required]. Approve for 1 year if the patient meets the following criteria (A and B):

B) Patient is ≥ 5 years of age; AND

C) The medication is prescribed by or in consultation with a physician who specializes in sickle cell disease (e.g., a hematologist).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Endari is not recommended in the following situations:

103. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

73. Endari™ oral powder [prescribing information]. Torrance CA: Emmaus Medical; October 2020.
74. Brandow AM, Carroll CP, Creary S, et al. American Society of Hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain. *Blood Adv*. 2020;4:2656-2701.
75. The National Institutes of Health – National Heart, Lung, and Blood Institute Evidence-Based Management of Sickle Cell Disease, Expert Panel Report 2014. Available at: https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf. Accessed on November 28, 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Sickle Cell Disease – Oxbryta Prior Authorization Policy
- Oxbryta® (voxelotor tablets, tablets for oral suspension – Global Blood Therapeutics)

REVIEW DATE: 12/07/2022

OVERVIEW

Oxbryta, a hemoglobin S (or sickle hemoglobin) polymerization inhibitor, is indicated for the treatment of **sickle cell disease** in patients ≥ 4 years of age.[1]

Guidelines

The American Society of Hematology guidelines for sickle cell disease: management of acute and chronic pain associated with sickle cell disease (2020) does not address the use of Oxbryta.[2] The National Institutes of Health – National Heart, Lung, and Blood Institute issued the Evidence-Based Management of Sickle Cell Disease, Expert Panel Report in 2014.[3] These guidelines were published prior to the approval of Oxbryta. Hydroxyurea has been shown to reduce the frequency of painful episodes, the incidence of acute coronary syndrome events, and the need for transfusions and hospitalizations.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Oxbryta. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Oxbryta as well as the monitoring required for adverse events and long-term efficacy, approval requires Oxbryta to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Oxbryta is recommended in those who meet the following criteria:

FDA-Approved Indication

19. Sickle Cell Disease. Approve for 1 year if the patient meets ONE of the following criteria (A or B):

D) Initial Therapy. Approve if the patient meets ALL of the following criteria (i, ii, iii, iv, and v):

- **i.** Patient is ≥ 4 years of age; AND
- **ii.** If the patient is ≥ 12 years of age, patient has had at least one sickle cell-related crisis in the previous 12-month period; AND
- **iii.** Patient's baseline hemoglobin level was ≤ 10.5 g/dL (before initiating Oxbryta therapy); AND
- **iv.** Patient meets one of the following criteria (a, b, or c):
  - **a)** Patient is currently receiving a hydroxyurea product; OR
  - **b)** According to the prescriber, patient has tried a hydroxyurea product and has experienced inadequate efficacy or significant intolerance; OR
  - **c)** According to the prescriber, patient is not a candidate for hydroxyurea therapy; AND

Note: Examples of patients who are not candidates for hydroxyurea therapy include patients who are pregnant or who are planning to become pregnant and patients with an immunosuppressive condition (such as cancer).

v. The medication is prescribed by or in consultation with a physician who specializes in sickle cell disease (e.g., a hematologist).

B) Patient is Currently Receiving Oxbryta. Approve for 1 year if the patient meets ALL of the following criteria (i, ii, and iii):

i. Patient is ≥ 4 years of age; AND

ii. According to the prescriber, patient is receiving clinical benefit from Oxbryta therapy; AND
Note: Examples of clinical benefit include reduction in the number of vaso-occlusive crises/sickle cell-related crises; delay in time to sickle cell-related crises; and reduction in the number of days in the hospital.

iii. The medication is prescribed by or in consultation with a physician who specializes in sickle cell disease (e.g., a hematologist).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Oxbryta is not recommended in the following situations:

72. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

76. Oxbryta™ tablets and tablets for oral suspension [prescribing information]. San Francisco, CA: Global Blood Therapeutics; October 2022.
77. Brandow AM, Carroll CP, Creary S, et al. American Society of Hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain. *Blood Adv*. 2020;4:2656-2701
78. The National Institutes of Health – National Heart, Lung, and Blood Institute Evidence-Based Management of Sickle Cell Disease, Expert Panel Report 2014. Available at: https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf. Accessed on November 28, 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Sohonos Prior Authorization Policy
- Sohonos™ (palovarotene capsules – Ipsen)

REVIEW DATE: 09/13/2023

OVERVIEW

Sohonos, a retinoid, is indicated for the reduction in volume of new heterotopic ossification in females ≥ 8 years of age and males ≥ 10 years of age with **fibrodysplasia ossificans progressiva**.[1]

Disease Overview

Fibrodysplasia ossificans progressiva is an ultra-rare, autosomal dominant genetic disorder of connective tissue characterized by progressive heterotopic ossification resulting in disability, immobility, and reduced quality/length of life.[2] Patients experience episodes of painful inflammatory swelling in soft tissues (flare-ups), some of which will spontaneously resolve, but most will transform soft connective tissues into mature heterotopic bone. Eventually, plates, sheets, and ribbons of heterotopic bone permanently replace muscles and connective tissue, encasing the patient almost like an armor, resulting in progressive and permanent immobility. There are no formal diagnostic criteria for fibrodysplasia ossificans progressiva.[2,3] A clinical diagnosis can be made in patients with great toe malformations, tissue swelling, and heterotopic ossification, but genetic confirmation of an Activin A Type 1 Receptor (ACVR1) gene mutation is needed. All patients with fibrodysplasia ossificans progressiva have a mutation in ACVR1, a gene encoding a bone morphogenetic protein type I receptor.[2,4] Approximately 97% of these patients have the same, heterozygous, single-nucleotide change in the glycine-serine activation domain of the ACVR1 ($ACVR1^{R206H}$).

Clinical Efficacy

In the pivotal study of Sohonos, patients were required to have fibrodysplasia ossificans progressiva as confirmed by a pathogenic variant in $ACVR1^{R206H}$.[1,5]

Guidelines

Medical management guidelines from the International Clinical Council on Fibrodysplasia Ossificans Progressiva and Consultants (2022) recommend that each patient with the disease should have a primary provider who is able to consult with an FOP expert and help coordinate a local care team.[2] The diagnosis of fibrodysplasia ossificans progressiva is based on clinical findings, but requires genetic confirmation (i.e., ACVR1 gene mutation), which can be detected by DNA sequence analysis.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Sohonos. All approvals are provided for the duration noted below. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: males are defined as individuals with the biological traits of a male, regardless of the individual's gender identity or gender expression; females are defined as individuals with the biological traits of a female, regardless of the individual's gender identity or gender expression. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sohonos as well as the monitoring required for adverse events and long-term efficacy, approval requires Sohonos to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sohonos is recommended in those who meet the following criteria:

FDA-Approved Indications

9. Fibrodysplasia ossificans progressiva. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient meets ONE of the following (i or ii):

i. Patient is female* and ≥ 8 years of age; OR

ii. Patient is male* and ≥ 10 years of age; AND

B) Patient has had a genetic test confirming a mutation in Activin A Type 1 Receptor (ACVR1)^{R206H} consistent with a diagnosis of fibrodysplasia ossificans progressiva; AND

C) Patient has heterotopic ossification as confirmed by radiologic testing; AND

HHH) Note: Examples of radiologic testing are x-ray, computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) scan.

D) The medication is prescribed by or in consultation with an endocrinologist or physician who specializes in bone disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sohonos is not recommended in the following situations:

73. Chronic Obstructive Pulmonary Disease (COPD). Sohonos is not indicated for the management of COPD.[1] Palovarotene was previously studied for the treatment of COPD, but was found to be ineffective for this condition.[4]

III)

74. Osteochondroma(s). Sohonos is not indicated for the treatment and/or prevention of osteochondroma.[1] One Phase II study was initiated to evaluate Sohonos for the prevention of disease progression in pediatric patients with multiple osteochondromas.[6] However, this study was terminated early in order to analyze accumulated data and evaluate the future of Sohonos for this use. Results are not available. More data are needed.

75. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

79. Sohonos™ capsules [prescribing information]. Cambridge, MA: Ipsen; August 2023.
80. Kaplan FS, Al Mukaddam M, Baujat G, et al, for the Internation council on FOP (ICC) & Consultants. The medical management of fibrodysplasia ossificans progressive: current treatment considerations. Updated May 2022. Available at: https://www.iccfop.org/dvlp/wp-content/uploads/2022/05/guidelines-updated-May-2022.pdf. Accessed on August 4, 2023.
81. Akesson LS, Svarirayan R, Adam MP, et al., editors. Fibrodysplasia ossificans progressiva. Gene Reviews® [Internet]. Seattle, WA: Univeristy of Washington, Seattle. Last revised May 11, 2023. Available at: https://www.ncbi.nlm.nih.gov/books/NBK558090/?report=printable. Accessed on August 4, 2023.
82. Pignolo RJ, Baujat G, Brown MA, et al. The natural of fibrodysplasia ossificans progressive: a prospective, global 36-month study. *Genet Med*. 2022;24(12):2422-2433.
83. Pignolo RJ, Hsiao EC, Mukaddam MA, et al. Reduction of new heterotopic ossification (HO) in the open-label, phase 3, MOVE trial of palovarotene for fibrodysplasia ossificans progressive (FOP). *J Bone Miner Res*. 2023;38(3):381-394.
84. US National Institutes of Health. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2023 Aug 4]. Available from: https://clinicaltrials.gov/. Search term: palovarotene.

PRIOR AUTHORIZATION POLICY

POLICY: Somatostatin Analogs – Mycapssa Prior Authorization Policy
- Mycapssa® (octreotide delayed-release capsules – Amryt)

REVIEW DATE: 10/11/2023

OVERVIEW
Mycapssa, a somatostatin analog, is indicated for long-term maintenance treatment in **acromegaly** patients who have responded to and tolerated treatment with octreotide or lanreotide.[1] Mycapssa maintained growth hormone and insulin-like growth factor 1 levels in patients with acromegaly.

GUIDELINES
The Endocrine Society Clinical Practice Guidelines for Acromegaly (2014) recommend medical therapy as adjuvant treatment after surgical intervention.[2] Mycapssa is not addressed in the guidelines. Primary medical therapy with somatostatin analogs (no preferred agent) can be recommended for some patients (e.g., surgery is not curative or patient is a poor surgical candidate). Updated recommendations to the 2014 guidelines on therapeutic outcomes for patients with acromegaly were created by the Acromegaly Consensus Group (2017).[3] The guidelines recommend Somatuline® Depot (lanreotide deep subcutaneous injection) and Sandostatin® LAR Depot (octreotide intramuscular injection) as first-line medical therapies in patients with persistent disease after surgery. Signifor® LAR (pasireotide intramuscular injection) is recommended as a second-line medical therapy due to its potential for hyperglycemic-associated adverse events. The Pituitary Society Acromegaly Management Guidelines (2020) recommend oral octreotide capsules as suitable for patients who have demonstrated complete or partial biochemical response to injectable octreotide or lanreotide.[4]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Mycapssa. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Mycapssa as well as the monitoring required for adverse events and long-term efficacy, approval requires Mycapssa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Mycapssa is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Acromegaly.** Approve for 1 year if the patient meets the following (A, B, and C):
   A) Patient has (or had) a pretreatment (baseline) insulin-like growth factor 1 (IGF-1) level above the upper limit of normal based on age and gender for the reporting laboratory; AND
   Note: Pretreatment (baseline) refers to the IGF-1 level prior to the initiation of a somatostatin analog (e.g., Mycapssa [octreotide delayed-release capsules], an octreotide acetate injection product [e.g., Bynfezia Pen, Sandostatin {generic}, Sandostatin LAR Depot], Signifor LAR

[pasireotide injection], Somatuline Depot [lanreotide injection], dopamine agonist [e.g., cabergoline, bromocriptine], or Somavert [pegvisomant injection]). Reference ranges for IGF-1 vary among laboratories.

B) According to the prescriber, patient has responded to one octreotide acetate injection product or Somatuline Depot (lanreotide injection); AND

C) The medication is prescribed by or in consultation with an endocrinologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mycapssa is not recommended in the following situations:

76. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

85. Mycapssa® capsules [prescribing information]. Scotland, UK: Amryt; March 2022.
86. Katznelson L, Laws ER Jr, Melmed S, et al; Endocrine Society. Acromegaly: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2014;99:3933-3951.
87. Melmed S, Bronstein M, Chanson P, et al. A consensus statement on acromegaly therapeutic outcomes. *Natural Reviews Endocrinology*. 2018;14(9):552-561.
88. Fleseriu M, Biller, BMK, Freda PU, et al. A Pituitary Society update to acromegaly management guidelines. *Pituitary*. 2020; 24:1-13.

PRIOR AUTHORIZATION POLICY

POLICY: Somatostatin Analogs – Lanreotide Products Prior Authorization Policy
- Lanreotide subcutaneous injection – Cipla
- Somatuline® Depot (lanreotide subcutaneous injection – Ipsen)

REVIEW DATE: 08/16/2023

OVERVIEW

The lanreotide products are somatostatin analogs indicated for the following uses:[1,2]

- **Acromegaly**, in patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy, is not an option. The goal of treatment in acromegaly is to reduce growth hormone and insulin-like growth factor-1 levels to normal.
- **Gastroenteropancreatic neuroendocrine tumors (GEP-NETs)**, in adult patients with unresectable, well or moderately differentiated, locally advanced or metastatic GEP-NETs to improve progression-free survival.

Additionally, Somatuline Depot is indicated for **carcinoid syndrome**, in adult patients.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for **neuroendocrine and adrenal tumors** (version 1.2023 – August 2, 2023) recommend Somatuline Depot for the management of carcinoid syndrome; tumors of the gastrointestinal tract, lung, thymus (carcinoid tumors), and pancreas (including glucagonomas, gastrinomas, VIPomas, insulinomas); pheochromocytomas; and paragangliomas.[3] Patients who have local unresectable disease and/or distant metastases and clinically significant tumor burden or progression should be started on therapy with a somatostatin analog to potentially control tumor growth.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of lanreotide products. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with lanreotide products as well as the monitoring required for adverse events and long-term efficacy, approval requires lanreotide products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of lanreotide products is recommended in those who meet one of the following criteria:

I. Coverage of Somatuline Depot is recommended in those who meet one of the following criteria:

FDA-Approved Indications

2. Acromegaly. Approve for 1 year if the patient meets the following (A, B, and C):
- **A)** Patient meets ONE of the following (i, ii, or iii):
  - **i.** Patient has had an inadequate response to surgery and/or radiotherapy; OR

ii. Patient is NOT an appropriate candidate for surgery and/or radiotherapy; OR
iii. Patient is experiencing negative effects due to tumor size (e.g., optic nerve compression); AND

B) Patient has (or had) a pre-treatment (baseline) insulin-like growth factor-1 (IGF-1) level above the upper limit of normal (ULN) based on age and gender for the reporting laboratory; AND
Note: Pre-treatment (baseline) refers to the IGF-1 level prior to the initiation of any somatostatin analog (e.g., Mycapssa [octreotide delayed-release capsules], an octreotide acetate injection product [e.g., Bynfezia Pen, Sandostatin {generics}, Sandostatin LAR Depot], Signifor LAR [pasireotide injection], Somatuline Depot [lanreotide injection], dopamine agonist [e.g., cabergoline, bromocriptine], or Somavert [pegvisomant injection]). Reference ranges for IGF-1 vary among laboratories.

C) The medication is prescribed by or in consultation with an endocrinologist.

2. **Carcinoid Syndrome.** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist, endocrinologist, or gastroenterologist.

3. **Neuroendocrine Tumor(s) [NETs] of the Gastrointestinal Tract, Lung, Thymus (Carcinoid Tumors), and Pancreas (including glucagonomas, gastrinomas, vasoactive intestinal peptides-secreting tumors [VIPomas], insulinomas).** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist, endocrinologist, or gastroenterologist.

Other Uses with Supportive Evidence

4. **Pheochromocytoma and Paraganglioma.** Approve for 1 year if the medication is prescribed by or in consultation with an endocrinologist, oncologist, or neurologist.

II. Coverage of lanreotide subcutaneous injection is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Acromegaly.** Approve for 1 year if the patient meets the following (A, B, and C):

A) Patient meets ONE of the following (i, ii, or iii):
i. Patient has had an inadequate response to surgery and/or radiotherapy; OR
ii. Patient is NOT an appropriate candidate for surgery and/or radiotherapy; OR
iii. Patient is experiencing negative effects due to tumor size (e.g., optic nerve compression); AND

B) Patient has (or had) a pre-treatment (baseline) insulin-like growth factor-1 (IGF-1) level above the upper limit of normal (ULN) based on age and gender for the reporting laboratory; AND
Note: Pre-treatment (baseline) refers to the IGF-1 level prior to the initiation of any somatostatin analog (e.g., Mycapssa [octreotide delayed-release capsules], an octreotide acetate injection product [e.g., Bynfezia Pen, Sandostatin {generics}, Sandostatin LAR Depot], Signifor LAR [pasireotide injection], Somatuline Depot [lanreotide injection], dopamine agonist [e.g., cabergoline, bromocriptine], or Somavert [pegvisomant injection]). Reference ranges for IGF-1 vary among laboratories.

C) The medication is prescribed by or in consultation with an endocrinologist.

2. **Neuroendocrine Tumor(s) [NETs] of the Gastrointestinal Tract, Lung, Thymus (Carcinoid Tumors), and Pancreas (including glucagonomas, gastrinomas, vasoactive intestinal peptides-secreting tumors [VIPomas], insulinomas).** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist, endocrinologist, or gastroenterologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of lanreotide products is not recommended in the following situations:

77. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

89. Somatuline® Depot subcutaneous injection [prescribing information]. Basking Ridge, NJ: Ipsen; February 2023.
90. Lanreotide subcutaneous injection [prescribing information]. Warren, NJ: Cipla; December 2021.
91. The NCCN Neuroendocrine and Adrenal Tumors Clinical Practice Guidelines in Oncology (version 1.2023 – August 2, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed August 17, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Somatostatin Analogs – Octreotide Immediate-Release Products Prior Authorization Policy
- Bynfezia Pen™ (octreotide acetate immediate-release subcutaneous injection – Sun Pharmaceutical [discontinued])
- Sandostatin® (octreotide acetate immediate-release subcutaneous or intravenous injection – Novartis, generic)

REVIEW DATE: 07/26/2023

OVERVIEW

Octreotide acetate immediate-release injection products (Bynfezia Pen, Sandostatin [generic]), somatostatin analogs, are indicated for the following uses:[1-3]

- **Acromegaly**, to reduce blood levels of growth hormone and insulin-like growth factor-1 in adults with acromegaly who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation, and bromocriptine mesylate at maximally tolerated doses.
- **Carcinoid tumors**, in adults with severe diarrhea and flushing episodes associated with metastatic carcinoid tumors. Studies were not designed to show an effect on the size, rate of growth, or development of metastases.
- **Vasoactive intestinal peptide (VIP) tumors**, in adults with profuse watery diarrhea associated with VIP-secreting tumors. Studies were not designed to show an effect on the size, rate of growth, or development of metastases.

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines support use of octreotide in multiple conditions.

- **Central Nervous System Cancers:** Guidelines (version 1.2023 – March 24, 2023) note that an octreotide scan may be used to confirm magnetic resonance imaging findings. NCCN also notes that everolimus and octreotide may be useful for patients with recurrent meningiomas.[4]
- **Neuroendocrine and Adrenal Tumors:** Guidelines (version 2.2022 – December 21, 2022) recommend octreotide for the management of carcinoid syndrome, tumors of the gastrointestinal tract, lung, thymus (carcinoid tumors), and pancreas (including glucagonomas, gastrinomas, VIPomas, insulinomas), pheochromocytomas, and paragangliomas.[5] Patients who have local unresectable disease and/or distant metastases and clinically significant tumor burden or progression should be started on therapy with a somatostatin analog to potentially control tumor growth.
- **Thymomas and Thymic Carcinomas:** Guidelines (version 1.2023 – December 15, 2022) note that in patients with thymoma who have positive octreotide scan or symptoms of carcinoid syndrome, octreotide therapy may be useful.[6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of octreotide immediate-release products. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with octreotide immediate-release products as well as the monitoring required for adverse events and long-term efficacy, approval requires octreotide

immediate-release products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of octreotide immediate-release products is recommended in those who meet one of the following criteria:

FDA-Approved Indications

3. Acromegaly. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **D)** Patient meets ONE of the following (i, ii, or iii):
  - **i.** Patient has had an inadequate response to surgery and/or radiotherapy; OR
  - **ii.** Patient is NOT an appropriate candidate for surgery and/or radiotherapy; OR
  - **iii.** Patient is experiencing negative effects due to tumor size (e.g., optic nerve compression); AND
- **E)** Patient has (or had) a pre-treatment (baseline) insulin-like growth factor-1 (IGF-1) level above the upper limit of normal based on age and gender for the reporting laboratory; AND
  Note: Pre-treatment (baseline) refers to the IGF-1 level prior to the initiation of any somatostatin analog (e.g., Mycapssa [octreotide delayed-release capsules], an octreotide acetate injection product [e.g., Bynfezia Pen, Sandostatin {generic}, Sandostatin LAR Depot], Signifor LAR [pasireotide injection], Somatuline Depot [lanreotide injection], dopamine agonist [e.g., cabergoline, bromocriptine], or Somavert [pegvisomant injection]). Reference ranges for IGF-1 vary among laboratories.
- **F)** The medication is prescribed by or in consultation with an endocrinologist.

2. Neuroendocrine Tumor(s) [NETs] of the Gastrointestinal Tract, Lung, Thymus (Carcinoid Tumors), and Pancreas (including glucagonomas, gastrinomas, vasoactive intestinal peptides-secreting tumors [VIPomas], insulinomas). Approve for 1 year if the medication is prescribed by or in consultation with an oncologist, endocrinologist, or gastroenterologist.

Other Uses with Supportive Evidence

5. Meningioma. Approve for 1 year if the medication is prescribed by or in consultation with an oncologist, radiologist, or neurosurgeon.

6. Pheochromocytoma and Paraganglioma. Approve for 1 year if the medication is prescribed by or in consultation with an endocrinologist, oncologist, or neurologist.

7. Thymoma and Thymic Carcinoma. Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of octreotide immediate-release products is not recommended in the following situations:

78. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

211. Bynfezia Pen™ subcutaneous injection [prescribing information]. Cranbury, NJ: Sun Pharmaceutical; April 2020.
212. Sandostatin® subcutaneous injection [prescribing information]. East Hanover, NJ: Novartis; October 2022.
213. Octreotide subcutaneous injection [prescribing information]. Parsippany, NJ: Teva; February 2023.
214. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 1.2023 – March 24, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 13, 2023.
215. The NCCN Neuroendocrine and Adrenal Tumors Clinical Practice Guidelines in Oncology (version 2.2022 – December 21, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 13, 2023.
216. The NCCN Thymomas and Thymic Carcinomas Clinical Practice Guidelines in Oncology (version 1.2023 – December 15, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 13, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Somatostatin Analogs – Sandostatin LAR Depot Prior Authorization Policy
- Sandostatin® LAR Depot (octreotide acetate intramuscular injection – Novartis)

REVIEW DATE: 08/16/2023

OVERVIEW

Sandostatin LAR Depot, a somatostatin analog, is indicated for the following uses:[1]

- **Acromegaly**, in patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy, is not an option. The goal of treatment in acromegaly is to reduce growth hormone and insulin-like growth factor-1 levels to normal.
- **Carcinoid tumors**, in patients with severe diarrhea and flushing episodes associated with metastatic carcinoid tumors.
- **Vasoactive intestinal peptide tumors (VIPomas)**, in patients with profuse watery diarrhea associated with vasoactive intestinal peptide (VIP)-secreting tumors.

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines support use of Sandostatin LAR Depot in multiple conditions:

- **Central Nervous System Cancers:** Guidelines (version 1.2023 – March 24, 2023) recommend Sandostatin LAR Depot for the treatment of meningiomas that recur despite surgery and/or radiation therapy, or are not amenable to treatment with surgery or radiation therapy.[2]
- **Neuroendocrine and Adrenal Tumors:** Guidelines (version 1.2023 – August 2, 2023) recommend Sandostatin LAR Depot for the management of carcinoid syndrome; tumors of the gastrointestinal tract, lung, thymus (carcinoid tumors), and pancreas (including glucagonomas, gastrinomas, VIPomas, insulinomas); pheochromocytomas; and paragangliomas.[3] Patients who have local unresectable disease and/or distant metastases and clinically significant tumor burden or progression should be started on therapy with a somatostatin analog to potentially control tumor growth. The North American Neuroendocrine Tumor Society (NANETS) consensus guidelines for the surveillance and medical management of midgut NETs (2017) also recommend Sandostatin LAR Depot as a first-line initial therapy in most patients with metastatic midgut NETs for control of carcinoid syndrome and inhibition of tumor growth.[4]
- **Thymomas and Thymic Carcinomas:** Guidelines (version 1.2023 – December 15, 2022) recommend Sandostatin LAR Depot as a therapy option with or without concomitant prednisone therapy.[5] In patients with thymoma who have positive octreotide scan or symptoms of carcinoid syndrome, octreotide therapy may be useful.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Sandostatin LAR Depot. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sandostatin LAR Depot as well as the monitoring required for adverse events and long-term efficacy, approval requires Sandostatin LAR Depot to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sandostatin LAR Depot is recommended in those who meet one of the following criteria:

FDA-Approved Indications

4. Acromegaly. Approve for 1 year if the patient meets the following (A, B, and C):
- **G)** Patient meets ONE of the following (i, ii, or iii):
  - **i.** Patient has had an inadequate response to surgery and/or radiotherapy; OR
  - **ii.** Patient is NOT an appropriate candidate for surgery and/or radiotherapy; OR
  - **iii.** Patient is experiencing negative effects due to tumor size (e.g., optic nerve compression); AND
- **H)** Patient has (or had) a pre-treatment (baseline) insulin-like growth factor-1 (IGF-1) level above the upper limit of normal based on age and gender for the reporting laboratory; AND
  Note: Pre-treatment (baseline) refers to the IGF-1 level prior to the initiation of any somatostatin analog (e.g., Mycapssa [octreotide delayed-release capsules], an octreotide acetate injection product [e.g., Bynfezia Pen, Sandostatin {generic}, Sandostatin LAR Depot], Signifor LAR [pasireotide injection], Somatuline Depot [lanreotide injection], dopamine agonist [e.g., cabergoline, bromocriptine], or Somavert [pegvisomant injection]). Reference ranges for IGF-1 vary among laboratories.
- **I)** The medication is prescribed by or in consultation with an endocrinologist.

2. Neuroendocrine Tumor(s) [NETs] of the Gastrointestinal Tract, Lung, Thymus (Carcinoid Tumors), and Pancreas (including glucagonomas, gastrinomas, vasoactive intestinal peptides-secreting tumors [VIPomas], insulinomas). Approve for 1 year if the medication is prescribed by or in consultation with an oncologist, endocrinologist, or gastroenterologist.

Other Uses with Supportive Evidence

8. Meningioma. Approve for 1 year if the medication is prescribed by or in consultation with an oncologist, radiologist, or neurosurgeon.

9. Pheochromocytoma and Paraganglioma. Approve for 1 year if the medication is prescribed by or in consultation with an endocrinologist, oncologist, or neurologist.

10. Thymoma and Thymic Carcinoma. Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sandostatin LAR Depot is not recommended in the following situations:

79. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

92. Sandostatin® LAR Depot intramuscular injection [prescribing information]. East Hanover, NJ: Novartis; July 2023.
93. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 1.2023 – March 24, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 28, 2023.
94. The NCCN Neuroendocrine and Adrenal Tumors Clinical Practice Guidelines in Oncology (version 1.2023 – August 2, 2023). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed August 17, 2023.
95. Strosberg JR, Halfdanarson TR, Bellizi AR, et al. The North American Neuroendocrine Tumor Society consensus guidelines for surveillance and medical management of midgut neuroendocrine Tumors. *Pancreas*. 2017;46(6):707-714.

96. The NCCN Thymomas and Thymic Carcinomas Clinical Practice Guidelines in Oncology (version 1.2023 – December 15, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 28, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Somatostatin Analogs – Signifor LAR Prior Authorization Policy
- Signifor® LAR (pasireotide intramuscular injection – Recordati Rare Diseases)

REVIEW DATE: 08/16/2023

OVERVIEW

Signifor LAR, a somatostatin analog, is indicated for the following uses:[1]

- **Acromegaly**, in patients who have had an inadequate response to surgery and/or for whom surgery is not an option. *In vivo* studies show that Signifor LAR lowers growth hormone and insulin-like growth factor-1 levels in patients with acromegaly.
- **Cushing's disease**, in patients for whom pituitary surgery is not an option or has not been curative.

Disease Overview

Cushing's syndrome refers to the general state of excessive levels of cortisol (hypercortisolism) in the blood.[2,3] Hypercortisolism can occur for reasons that are either endogenous or exogenous in nature (e.g., Cushing's disease, cortisol-containing medications, adrenal gland tumor, certain cancers). Cushing's disease (hypercortisolism caused by pituitary adenomas) is the most common type of adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome. Treatment for Cushing's syndrome requires a multi-modal approach. The goals of treatment are normalization of cortisol excess, long-term disease control, avoidance of recurrence, and reversal of clinical features.[4]

Guidelines

The Endocrine Society published clinical practice guidelines for the treatment of Cushing's syndrome in (2015) and Cushing's disease (2021).[5,6] Recorlev is recognized in the 2021 guidelines for Cushing's disease as investigational; further details regarding this therapy are not discussed. Treatment goals for Cushing's syndrome are to normalize cortisol levels or its action at the receptors to eliminate signs and symptoms of Cushing's syndrome. Best practice adjunctive management include treating co-morbidities associated with hypercortisolism (psychiatric disorders, diabetes, hypertension, hypokalemia, infections, dyslipidemia, osteoporosis, and poor physical fitness). First-line treatment involves resection of the tumor, unless surgery is not possible or is unlikely to meaningfully reduce excess glucocorticoid. Specifically for Cushing's disease, transsphenoidal selective adenomectomy by a surgeon with extensive experience in pituitary surgery is recommended. In patients with ACTH-dependent Cushing's syndrome who underwent noncurative surgery or for whom surgery was not possible, the guidelines advocate several second-line therapies (e.g., repeat transsphenoidal surgery, radiotherapy, medical therapy, and bilateral adrenalectomy). For Cushing's disease, the guidelines recommend all medical therapies as second-line options after transsphenoidal surgery. These involve steroidogenesis inhibitors (ketoconazole, Metopirone® [metyrapone capsules], Lysodren® [mitotane tablets], etomidate) in patients either with or without radiotherapy/radiosurgery; pituitary-directed medical treatments (cabergoline, Signifor® [pasireotide subcutaneous injection]) in patients who are not surgical candidates or who have persistent disease; and Korlym® (mifepristone tablets) in patients with diabetes or glucose intolerance who are not surgical candidates or who have persistent disease after transsphenoidal surgery.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Signifor LAR. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Signifor LAR as well as the monitoring required for adverse events and long-term efficacy, approval requires Signifor LAR to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Signifor LAR is recommended in those who meet one of the following criteria:

FDA-Approved Indications

5. Acromegaly. Approve for 1 year if the patient meets the following (A, B, and C):
- **J)** Patient meets ONE of the following (i, ii, or iii):
  - **i.** Patient has had an inadequate response to surgery and/or radiotherapy; OR
  - **ii.** Patient is NOT an appropriate candidate for surgery and/or radiotherapy; OR
  - **iii.** Patient is experiencing negative effects due to tumor size (e.g., optic nerve compression); AND
- **K)** Patient has (or had) a pre-treatment (baseline) insulin-like growth factor-1 (IGF-1) level above the upper limit of normal based on age and gender for the reporting laboratory; AND
  Note: Pre-treatment (baseline) refers to the IGF-1 level prior to the initiation of any somatostatin analog (e.g., Mycapssa [octreotide delayed-release capsules], an octreotide acetate injection product [e.g., Bynfezia Pen, Sandostatin {generic}, Sandostatin LAR Depot], Signifor LAR [pasireotide injection], Somatuline Depot [lanreotide injection], dopamine agonist [e.g., cabergoline, bromocriptine], or Somavert [pegvisomant injection]). Reference ranges for IGF-1 vary among laboratories.
- **L)** The medication is prescribed by or in consultation with an endocrinologist.

2. Cushing's Disease. Approve for the duration noted if the patient meets the following (A or B):
- **A)** Initial Therapy. Approve for 4 months of initial therapy if the patient meets the following (i and ii):
  - **i.** According to the prescriber, patient is not a candidate for surgery, or surgery has not been curative; AND
    Note: For patients with Cushing's disease/syndrome awaiting surgery, see *Other Uses with Supportive Evidence.*
  - **ii.** Signifor LAR is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's disease.
- **B)** Patient is Currently Receiving Signifor LAR/Signifor. Approve for 1 year of continuation therapy if the patient has responded to Signifor/Signifor LAR, as determined by the prescriber.
  Note: An example of patient response is decrease in the mean urinary free cortisol level.

Other Uses with Supportive Evidence

3. Endogenous Cushing's Syndrome – Patient Awaiting Surgery. Approve for 4 months if Signifor LAR is prescribed by or in consultation with an endocrinologist or a physician who specialized in the treatment of Cushing's syndrome.

4. **Endogenous Cushing's Syndrome – Patient Awaiting Therapeutic Response After Radiotherapy.** Approve for 4 months if Signifor LAR is prescribed by or in consultation with an endocrinologist or a physician who specialized in the treatment of Cushing's syndrome.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Signifor LAR is not recommended in the following situations:

80. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

97. Signifor® LAR subcutaneous injection [prescribing information]. Lebanon, NJ: Recordati Rare Diseases; July 2021.
98. Sharma ST, Nieman LK, Feelders RA. Cushing's syndrome: epidemiology and developments in disease management. *Clin Epidemiol*. 2015;7:281–293.
99. Tritos NA, Biller BM. Advances in medical therapies for Cushing's syndrome. *Discov Med*. 2012;13(69):171-179.
100. Biller BMK, Grossman AB, Stewart PM, et al. Treatment of adrenocorticotropin-dependent Cushing's syndrome: A consensus statement. *J Clin Endocrinol Metab*. 2008;93:2454-2462.
101. Nieman LK, Biller BM, Findling JW. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2015;100(8):2807-2831.
102. Fleseriu M, Auchus R, Bancos I, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. *Lancet Diabetes Endocrinol*. 2021;9(12):847-875.

PRIOR AUTHORIZATION POLICY

POLICY: Somavert Prior Authorization Policy
- Somavert® (pegvisomant subcutaneous injection – Pfizer)

REVIEW DATE: 08/23/2023

OVERVIEW

Somavert, a growth hormone receptor antagonist, is indicated for the treatment of **acromegaly** in patients who have had inadequate response to surgery and/or radiation therapy and/or other medical therapies, or for whom these therapies are not appropriate.[1] The goal of treatment is to normalize serum insulin-like growth factor-1 levels.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Somavert. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Somavert as well as the monitoring required for adverse events and long-term efficacy, approval requires Somavert to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Somavert is recommended in those who meet the following criteria:

FDA-Approved Indication

6. Acromegaly. Approve for 1 year if the patient meets the following (A, B, and C):

M) Patient meets ONE of the following (i, ii, or iii):
- **i.** Patient has had an inadequate response to surgery and/or radiotherapy; OR
- **ii.** Patient is NOT an appropriate candidate for surgery and/or radiotherapy; OR
- **iii.** Patient is experiencing negative effects due to tumor size (e.g., optic nerve compression); AND

N) Patient has (or had) a pre-treatment (baseline) insulin-like growth factor-1 (IGF-1) level above the upper limit of normal based on age and gender for the reporting laboratory; AND
Note: Pre-treatment (baseline) refers to the IGF-1 level prior to the initiation of any somatostatin analog (e.g., Mycapssa [octreotide delayed-release capsules], an octreotide acetate injection product [e.g., Bynfezia Pen, Sandostatin {generics}, Sandostatin LAR Depot], Signifor LAR [pasireotide intramuscular injection], Somatuline Depot [lanreotide subcutaneous injection]), dopamine agonist (e.g., cabergoline, bromocriptine), or Somavert.

O) The medication is prescribed by or in consultation with an endocrinologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Somavert is not recommended in the following situations:

81. Treatment of Excess Growth Hormone Associated with McCune-Albright Syndrome. Five patients with growth hormone excess due to McCune-Albright Syndrome were treated with 20 mg of Somavert daily for 12 weeks in a randomized, double-blind, placebo-controlled trial at the National Institutes of Health.[2] Somavert reduced IGF-1 and IGF binding protein-3 in these patients but had no effect on fibrous dysplasia.

82. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

217. Somavert® subcutaneous injection [prescribing information]. New York, New York: Pfizer; July 2023.
218. Akintoye SO, Kelly MH, Brillante B, et al. Pegvisomant for the treatment of gsp-mediated growth hormone excess in patients with McCune-Albright Syndrome. *J Clin Endocrinol Metab*. 2006;91:2960-2966.

PRIOR AUTHORIZATION POLICY

POLICY: Spinal Muscular Atrophy – Evrysdi Prior Authorization Policy
- Evrysdi® (risdiplam oral solution – Genentech/Roche)

REVIEW DATE: 11/01/2023

OVERVIEW
Evrysdi, a survival motor neuron (SMN)2 splicing modifier, is indicated for the **treatment of spinal muscular atrophy** in pediatric patients and adults.[1] The recommended dosing is as follows:
- 0.15 mg/kg once daily (QD) for patients < 2 months of age.
- 0.2 mg/kg QD for patients 2 months to < 2 years of age.
- 0.25 mg/kg QD for patients ≥ 2 years of age and < 20 kg.
- 5 mg QD for patients ≥ 2 years of age and ≥ 20 kg.

Disease Overview
Spinal muscular atrophy is a genetic, autosomal recessive muscular disorder caused by deletion or loss of function mutation in the SMN1 gene.[2-5] The reduced level of SMN protein causes degeneration of lower motor neurons.[5] The phenotypic expression of the disease is impacted by the SMN2 gene copy number. Data have shown that patients with a higher number of SMN2 copies generally have a more mild phenotypic disease expression. Gene deletion testing for spinal muscular atrophy can be performed at many diagnostic laboratories. Table 1 describes the disease types. Of note, various motor ability assessments are used in clinical practice to characterize functional impairment in spinal muscular atrophy. Different functional motor scales are utilized to evaluate patients.[6] When motor neuron function is lost, it cannot be regained, which greatly impacts patients who have experienced progression (e.g., patients with complete paralysis of limbs or permanent ventilator dependence).[1-6]

Table 1. Types of Spinal Muscular Atrophy.[2-5]
SMA – Spinal muscular atrophy; SMN2 – Survival motor neuron 2.

In addition to Evrysdi, other therapies are available. **Spinraza®** (nusinersen intrathecal injection), a SMN2-directed antisense oligonucleotide, is indicated for the treatment of spinal muscular atrophy in pediatric patients and adults.[7] Although studies and experience continue, the primary pivotal data include infantile-onset (Type 1) and later-onset (Type 2 and Type 3) spinal muscular atrophy primarily in children. Data are also available with Spinraza in presymptomatic infants who were genetically diagnosed with spinal muscular atrophy. There are some data with Spinraza in adults as well.

Zolgensma® (onasemnogene abeparvovec-xioi intravenous infusion), an adeno-associated virus vector-based gene therapy, is indicated for the treatment of pediatric patients < 2 years of age with spinal muscular atrophy with bi-allelic mutations in the SMN1 gene.[7] The agent works by providing a copy of the gene encoding the SMN protein, which increases its production. Zolgensma is administered as a single-dose intravenous infusion over 60 minutes. Pivotal studies mainly involved infants with two or three SMN2 gene copies with primarily Type 1 or Type 2 disease.

Clinical Efficacy
The efficacy of Evrysdi for the treatment of patients with infantile-onset (Type 1), later-onset (Type 2 and 3), and pre-symptomatic spinal muscular atrophy was evaluated in three clinical studies.[1,9-11] **FIREFISH** involved patients with Type 1 spinal muscular atrophy who had symptom onset between 28 days and 3

months of age.[1] Genetic confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the SMN1 gene was required for trial entry. Patients had two SMN2 gene copies. Many patients gained improvements in the ability to sit for at least 5 seconds independently, and there was an increase in the percentages of patients who were alive without permanent ventilation. **SUNFISH** evaluated Evrysdi in patients with later-onset (Type 2 or Type 3) spinal muscular atrophy. Most patients (90%) had three SMN2 gene copies; 8% and 2% of patients had four and two SMN2 gene copies, respectively. In Part 2 of the study, benefits of Evrysdi vs. placebo were noted at Month 12 in motor function as well as in upper limb motor performance. **RAINBOWFISH** investigated Evrysdi in infants up to 6 weeks of age (at the first dose) who had been genetically diagnosed with spinal muscular atrophy but did not have symptoms. In total, seven patients have received Evrysdi for at least 12 months. Four patients had two SMN2 copies, two patients had three SMN2 gene copies, and one patient had four or more SMN2 copies. The median age at first dose among the seven patients was 35 days. The six patients with two or three SMN2 gene copies achieved various motor milestones at Month 12, including the ability to sit. Of note, in general, the onset of effect with Evrysdi was observed after approximately 4 months of therapy. Evrysdi has not been evaluated in patients with fewer than two or more than four SMN2 gene copies.[1,9-11]

Guidelines

Evrysdi is not addressed in guidelines. According to a treatment algorithm from the Spinal Muscular Atrophy Newborn Screening Multidisciplinary Working Group (2018), immediate treatment is recommended in patients with two or three SMN2 gene copies.[12] In 2020, the Working Group updated recommendations that infants diagnosed with spinal muscular atrophy via newborn screening with four SMN2 gene copies should receive immediate treatment.[13] Patients with five (or more) SMN2 gene copies should be observed and screened for symptoms.

Safety

Based on animal data, Evrysdi may cause fetal harm if given to a pregnant woman.[1] Pregnancy testing is recommended for females of reproductive potential prior to initiating Evrysdi. Advise females of reproductive potential to use effective contraception during treatment with Evrysdi and for at least 1 month after the last dose.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Evrysdi. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Evrysdi as well as the monitoring required for adverse events and long-term efficacy, approval requires Evrysdi to be prescribed by a physician who has consulted with or who specializes in the condition. For certain criteria, verification is required as noted by **[verification in claims history required]**. In the criteria for Evrysdi, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: females are defined as individuals with the biological traits of a woman, regardless of the individual's gender identity or gender expression. All reviews will be forwarded to the Medical Director for evaluation.

Automation: None.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information. In subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *Spinal Muscular Atrophy – Evrysdi Prior Authorization Policy* through the Coverage Review Department, and who is requesting reauthorization, the criteria utilized do

NOT require resubmission of documentation for reauthorization, except for the criterion requiring documentation of response or benefit to Evrysdi therapy.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Evrysdi is recommended in those who meet the following criteria:

FDA-Approved Indication

10. Spinal Muscular Atrophy – Treatment. Approve if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets all of the following criteria (i, ii, iii, iv, v, vi, vii, and viii):

i. Baseline motor ability assessment that suggests spinal muscular atrophy (based on age, motor ability, and development) has been performed from one of the following exams (a, b, c, d, e, f, or g) **[documentation required]**:

a) Bayley Scales of Infant and Toddler Development; OR

b) Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND); OR

c) Hammersmith Functional Motor Scale Expanded (HFMSE); OR

d) Hammersmith Infant Neurological Exam Part 2 (HINE-2); OR

e) Motor Function Measure-32 Items (MFM-32); OR

f) Revised Upper Limb Module (RULM) test; OR

g) World Health Organization motor milestone scale; AND

ii. Patient has had a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic pathogenic variants in the survival motor neuron 1 (SMN1) gene **[documentation required]**; AND

JJJ) Note: Pathogenic variants may include homozygous deletion, compound heterozygous mutation, or a variety of other rare mutations.

iii. Patient meets one of the following criteria (a or b):

a) Patient has two or three survival motor neuron 2 (SMN2) gene copies **[documentation required]**; OR

b) Patient meets both of the following ([1] and [2]):

(1) Patient has four survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND

(2) Patient has objective signs consistent with spinal muscular atrophy Types 1, 2, or 3 **[documentation required]**; AND

iv. For a patient currently receiving or who has received prior treatment with Spinraza (nusinersen intrathecal injection), the prescribing physician confirms that further therapy with Spinraza will be discontinued; AND

v. Patient has not received Zolgensma (onasemnogene abeparvovec-xioi intravenous infusion) in the past **[verification in claims history required]**; AND

KKK) Note: Verify through claims history that the patient has NOT previously received Zolgensma. If no claim for Zolgensma is present, the prescribing physician confirms that the patient has not previously received Zolgensma.

vi. According to the prescribing physician, a female* patient of reproductive potential must meet both the following criteria (a and b):

a) Patient is not currently pregnant; AND

b) Effective contraception will be utilized during treatment and for 1 month after the last Evrysdi dose; AND

vii. Dosing of Evrysdi meets ONE of the following criteria based on the current (within the past 1 month) kg weight of the patient (a, b, c, or d):
- **a)** 0.15 mg/kg once daily if the patient is < 2 months of age; OR
- **b)** 0.2 mg/kg once daily if the patient is 2 months to < 2 years of age; OR
- **c)** 0.25 mg/kg once daily if the patient is ≥ 2 years of age and weighs < 20 kg; OR
- **d)** 5 mg once daily if the patient is ≥ 2 years of age and weighs ≥ 20 kg; AND

viii. The medication is prescribed by a physician who has consulted with a specialist or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; OR

B) Patient Currently Receiving Evrysdi. Approve for 4 months if the patient meets all of the following criteria (i, ii, iii, iv, v, vi, vii, and viii):

i. Patient has had a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic pathogenic variants in the survival motor neuron 1 (SMN1) gene **[documentation required]**; AND

LLL) Note: Pathogenic variants may include homozygous deletion, compound heterozygous mutation, or a variety of other rare mutations.

ii. Patient meets one of the following criteria (a or b):
- **a)** Patient has two or three survival motor neuron 2 (SMN2) gene copies **[documentation required]**; OR
- **b)** Patient meets both of the following criteria [(1) and (2)]:
  - **(1)** Patient has four survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND
  - **(2)** Patient has objective signs consistent with spinal muscular atrophy Types 1, 2, or 3 **[documentation required]**; AND

iii. For a patient currently receiving or who has received prior treatment with Spinraza (nusinersen intrathecal injection), the prescribing physician confirms that further therapy with Spinraza will be discontinued; AND

iv. Patient has not received Zolgensma (onasemnogene abeparvovec-xioi intravenous infusion) in the past **[verification in claims history required]**; AND

MMM) Note: Verify through claims that the patient has NOT previously received Zolgensma. If no claim for Zolgensma is present, the prescribing physician confirms that the patient has not previously received Zolgensma.

v. According to the prescribing physician, a female* patient of reproductive potential must meet both the following criteria (a and b):
- **a)** Patient is not currently pregnant; AND
- **b)** Effective contraception will be utilized during treatment and for 1 month after the last Evrysdi dose; AND

vi. Dosing of Evrysdi meets ONE of the following criteria based on the current (within the past 1 month) kg weight of the patient (a, b, c, or d):
- **a)** 0.15 mg/kg once daily if the patient is < 2 months of age; OR
- **b)** 0.2 mg/kg once daily if the patient is 2 months to < 2 years of age; OR
- **c)** 0.25 mg/kg once daily if the patient is ≥ 2 years of age and weighs < 20 kg; OR
- **d)** 5 mg once daily if the patient is ≥ 2 years of age and weighs ≥ 20 kg; AND

vii. The medication is prescribed by a physician who has consulted with a specialist or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; AND

viii. Patient must meet one of the following criteria (a or b):
- **a)** Patient must have had a positive clinical response (for example, improvement or stabilization) from pretreatment baseline status (i.e., within the past 4 months) with Evrysdi in one of the following exams [(1), (2), (3), (4), (5), (6), or (7)] **[documentation required]**:

(1) Bayley Scales of Infant and Toddler Development; OR
(2) Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND); OR
(3) Hammersmith Functional Motor Scale Expanded (HFMSE); OR
(4) Hammersmith Infant Neurological Exam Part 2 (HINE-2); OR
(5) Motor Function Measure-32 Items (MFM-32); OR
(6) Revised Upper Limb Module (RULM) test; OR
(7) World Health Organization motor milestone scale; OR

b) According to the prescribing physician, the patient has responded to Evrysdi and continues to benefit from ongoing Evrysdi therapy by the most recent (i.e., within the past 4 months) physician monitoring/assessment tools **[documentation required]**.

NNN) Note: Examples include pulmonary function tests showing improvement, bulbar function test results suggesting benefits, reduced need for respiratory support, decrease in the frequency of respiratory infections or complications, and/or prevention of permanent assisted ventilation.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Evrysdi is not recommended in the following situations:

83. Patient has Complete Paralysis of All Limbs. Data are needed to determine if this patient population with advanced spinal muscular atrophy would derive benefits from Evrysdi.
OOO)

84. Patient has Permanent Ventilator Dependence. Data are needed to determine if this patient population with advanced spinal muscular atrophy would derive benefits from Evrysdi.
PPP)

85. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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104. Arnold ES, Fischbeck KH. Spinal muscular atrophy. *Handb Clin Neurol*. 2018;148:591-601.
105. Prior TW, Leach ME, Finanger E. Spinal Muscular Atrophy. 2000 Feb 24 [Updated 2020 December 3]. In: Adam MP, Ardinger, HH, Pagon RA, et al, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1352/. Accessed on March 22, 2023.
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PRIOR AUTHORIZATION POLICY

POLICY: Spinal Muscular Atrophy – Gene Therapy – Zolgensma Prior Authorization Policy
- Zolgensma® (onasemnogene abeparvovec-xioi intravenous infusion – Novartis)

REVIEW DATE: 11/01/2023

OVERVIEW

Zolgensma, an adeno-associated virus vector-based gene therapy, is indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.[1]

Limitations of use are that the safety and effectiveness of repeat administration of Zolgensma have not been evaluated.[1] The use of Zolgensma in patients with advanced spinal muscular atrophy (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been assessed. Use of Zolgensma in premature neonates before reaching full-term gestational age is not recommended because concomitant treatment with corticosteroids may adversely affect neurological development. Zolgensma therapy should be delayed until full-term gestational age is achieved. The definition of full-term pregnancy commences at 39 weeks and 0 days gestation.[2]

Disease Overview

Spinal muscular atrophy is a genetic, autosomal recessive muscular disorder caused by deletion or loss of function mutation in the SMN1 gene.[3-6] The reduced levels of survival motor neuron (SMN) protein causes degeneration of lower motor neurons.[6] Although the condition is a multisystem disorder, it is clinically characterized by progressive muscle weakness and atrophy. Patients have difficulties with ambulation, head control, feeding, and respiration. Cognitive development is not impacted. In the US, spinal muscular atrophy affects approximately one in 11,000 infants and has an average carrier frequency of one in 54 individuals; as many as 10,000 to 20,000 children and adults in the US may be impacted.[6] Although the condition can be present in individuals of any age, it is more frequently diagnosed in infants and children, as it is more severe in this population.[3-6] The phenotypic expression of the disease is impacted by the presence of the survival motor neuron 2 (SMN2) gene copy number. SMN1 is responsible for producing most of the effective SMN protein, although some SMN protein can be made by the SMN2 gene. Therefore, patients with a deletion of the SMN1 gene may have the potential for making some SMN protein through the SMN2 gene copy, although in most cases the resulting protein made by this gene is truncated and is not as effective or functional. Data have shown that patients with a higher number of SMN2 gene copies generally have a more mild phenotypic disease expression. Gene deletion testing for spinal muscular atrophy can be performed at many diagnostic laboratories. Table 1 describes disease types. A different manner of categorization classifies the three most common types as follows: Type 1 patients are "non-sitters", Type 2 patients are "sitters", and Type 3 patients are "walkers".[4,6]

Table 1. Types of Spinal Muscular Atrophy.[3-6]

Table 1 (continued). Types of Spinal Muscular Atrophy.[3-6]
SMA – Spinal muscular atrophy; SMN2 – Survival motor neuron 2.

Besides Zolgensma, other therapies are available. **Spinraza®** (nusinersen intrathecal injection), a SMN2-directed antisense oligonucleotide, is indicated for the treatment of spinal muscular atrophy in pediatric and adult patients.[7] Spinraza is given by intrathecal injection. Although studies and experience continue, the primary pivotal data include infantile-onset (Type 1) and later-onset (Type 2 and Type 3) spinal muscular

atrophy primarily in children. Data are also available with Spinraza in presymptomatic infants who were genetically diagnosed with spinal muscular atrophy. There is an accumulation of data with Spinraza in adults as well.

Evrysdi® (risdiplam oral solution), a SMN2 splicing modifier, is indicated for the treatment of spinal muscular atrophy in pediatric and adult patients.[8] The primary pivotal data include infantile-onset (Type 1) and later-onset (Type 2 and Type 3) spinal muscular atrophy primarily in children and adults up to 25 years of age. Trials are ongoing in older adults, as well as in presymptomatic infants who were genetically diagnosed with spinal muscular atrophy.

Clinical Efficacy

The efficacy of Zolgensma was evaluated in patients less than 2 years of age with spinal muscular atrophy who had bi-allelic mutations in the SMN1 gene.[1,9-14] One trial was an open-label, single-arm study which is ongoing (STR1VE [n = 21])[11] and the other was an open-label, single-arm, ascending-dose clinical trial (START [n = 15] {12 patients received a therapeutic dose}).[1,9,10] Symptoms onset occurred before patients were 6 months of age. All patients had genetically confirmed bi-allelic SMN1 gene deletions and two SMN2 gene copies. In both trials, Zolgensma was given as a single-dose intravenous infusion. Efficacy was assessed on parameters such as survival and achievement of developmental motor milestones (e.g., sitting without support). The definition of survival was the time from birth to either death or permanent ventilation. Other efficacy parameters were evaluated (e.g., assessment of Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders [CHOP-INTEND] scores, evaluation of ventilator use). The ongoing clinical trial involved 21 patients with infantile-onset spinal muscular atrophy. The mean CHOP-INTEND score was 31.0 (range, 18 to 47). The mean patient age at the time of treatment was 3.9 months (range 0.5 to 5.9 months). As of the March 2019 cutoff date, 19 patients were alive without permanent ventilation. Compared with natural history data, Zolgensma is effective as more patients attained the ability to sit without support.[1] The completed clinical trial involved 15 patients with infantile-onset spinal muscular atrophy.[1,9] Three patients were in a low-dose cohort and 12 patients were in a high-dose cohort.[1] At the time of treatment, the mean age of patients in the low-dose cohort was 6.3 months (range 5.9 to 7.2 months) and 3.4 months (range 0.9 to 7.9 months) in the high-dose group. The dose in the low-dose cohort was approximately one-third of the dosage received by patients in the high-dose cohort. At 24 months following Zolgensma infusion, one patient in the low-dose cohort met the endpoint of permanent ventilation; all 12 patients in the high-dose cohort were alive without permanent ventilation. In the high-dose cohort, 9 of 12 patients (75%) were able to stand and walk without assistance.[1,9] At longer-term follow-up from the START trial, all 10 patients followed in the high-dose group were alive without permanent ventilation at the dataset on June 11, 2020. In STR1VE, at the March 2019 data cutoff, 19 patients were alive without permanent ventilation.[1] Up until November 2019, data revealed that 13 of 22 patients achieved the coprimary endpoint of functional independent sitting for 30 seconds or longer at the 18 months of age study visit.[11] Other data are also available.[12-15]

Guidelines

The Spinal Muscular Atrophy Newborn Screening Multidisciplinary Working Group is comprised of clinicians and geneticists with expertise in spinal muscular atrophy who developed a treatment algorithm in 2018 for infants who have positive results from a newborn screening test for spinal muscular atrophy.[16] Spinal muscular atrophy Types 1 and 2 comprise a large majority of cases and account for many patients who screen positively for spinal muscular atrophy with three or fewer SMN2 gene copies. Immediate treatment is recommended in patients with two or three SMN2 gene copies. Treatment recommendations for patients who screen positive for spinal muscular atrophy and have only one SMN2 gene copy are more complicated. It is likely that patients with only one SMN2 gene copy will likely be symptomatic at birth and the physician should determine if treatment is warranted.[16] In 2020, the Working Group updated recommendations that infants diagnosed with spinal muscular atrophy via newborn screening with four

SMN2 gene copies should receive immediate treatment.[17] Also, patients with five (or more) SMN2 gene copies should be observed and screened for symptoms.

Dosing

The recommended dose of Zolgensma is 1.1×10^{14} vector genomes (vg) per kg of body weight.[1] Administer Zolgensma as an intravenous infusion over 60 minutes. Starting 1 day prior to Zolgensma infusion, give systemic corticosteroids equivalent to oral prednisolone 1 mg/kg of body weight for a total of 30 days. Examine liver function after this juncture and follow recommended guidelines.

Safety

Zolgensma has a Boxed Warning regarding acute serious liver injury and acute liver failure.[1] Elevated aminotransferases can occur with Zolgensma. Patients with preexisting liver impairment may be at higher risk. Prior to infusion, evaluate liver function in all patients by clinical examination and laboratory testing. One day before Zolgensma infusion, commence administration of systemic corticosteroids equivalent to oral prednisolone at 1 mg/kg of body weight per day for a total of 30 days. Prior to administration of Zolgensma, evaluate creatinine and complete blood counts. Perform baseline anti-AAV9 antibody testing prior to Zolgensma infusion. Patients in the Zolgensma trials were required to have baseline anti-AAV9 antibody titers of $\leq$ 1:50.

POLICY STATEMENT

Prior Authorization is recommended for benefit coverage of Zolgensma. Approval is recommended for those who meet the Criteria for the listed indication. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zolgensma as well as the specialized training required for administration of Zolgensma, approval requires Zolgensma to be prescribed by a physician who has consulted with or who specializes in the condition. All approvals are provided for one dose per lifetime. The approval duration is 1 month to allow for an adequate timeframe to prepare and administer one dose of therapy. For certain criteria, verification is required as noted by **[verification in claims history required]**. All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation.

Some clients have elected Embarc Benefit Protection. For these clients, the Medical Director will coordinate with eviCore to ensure the Embarc Benefit Protection portion of the review has been completed. If the Embarc Benefit Protection portion of the review has not been completed, the Medical Director will route to Embarc@eviCore.com prior to completing the review.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to chart notes, laboratory tests, claims records, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zolgensma is recommended in those who meet the following criteria:

FDA-Approved Indication

D) Spinal Muscular Atrophy – Treatment. Approve for a one-time per lifetime dose if the patient meets the following (A, B, C, D, E, F, G, H, I, J, K, L, M, and N):

- **i.** Patient is less than 2 years of age; AND

ii. If the patient is a premature neonate, full-term gestational age of 39 weeks and 0 days has been met; AND

Note: Full-term gestational age can be defined as the postmenstrual age (gestational age plus chronological age) being equal to ≥ 39 weeks and 0 days.

iii. Patient has had a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic pathogenic variants in the survival motor neuron 1 (SMN1) gene **[documentation required]**; AND

Note: Pathogenic variants may include homozygous deletion, compound heterozygous mutation, or a variety of other rare mutations.

iv. Patient meets one of the following (i or ii):

a) Patient has three or fewer survival motor neuron 2 (SMN2) gene copies **[documentation required]**; OR

b) Patient meets both of the following (a and b):

i. Patient has four survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND

ii. The number of survival motor neuron 2 (SMN2) gene copies has been determined by a quantitative assay capable of distinguishing between four SMN2 gene copies and five or greater SMN2 gene copies; AND

v. According to the prescribing physician, patient has started or will receive systemic corticosteroids equivalent to oral prednisolone at a dose of 1 mg/kg per day commencing 1 day prior to Zolgensma infusion for a total of 30 days; AND

vi. Baseline anti-AAV9 antibody titers are ≤ 1:50 **[documentation required]**; AND

vii. Patient has undergone a liver function assessment within the last 30 days and meets all of the following (i, ii, iii, and iv):

a) Alanine aminotransferase levels are ≤ 2 times the upper limit of normal **[documentation required]**; AND

b) Aspartate aminotransferase levels are ≤ 2 times the upper limit of normal **[documentation required]**; AND

c) Total bilirubin levels are ≤ 2 times the upper limit of normal **[documentation required]**; AND

Note: Patient with elevated bilirubin levels due to neonatal jaundice are acceptable.

d) Prothrombin time results are ≤ 2 times the upper limit of normal **[documentation required]**; AND

viii. Patient has undergone a renal function assessment within the last 30 days and has a creatinine level < 1.0 mg/dL **[documentation required]**; AND

ix. A complete blood count has been obtained within the last 30 days and the patient meets both of the following (i and ii):

a) White blood cell count is ≤ 20,000 cells per mm^3 **[documentation required]**; AND

b) Hemoglobin levels are between 8 g/dL and 18 g/dL **[documentation required]**; AND

x. Patient has not received Zolgensma in the past **[verification in claims history required]**; AND

Note: Verify through claims that the patient has not previously received Zolgensma. If no claim for Zolgensma is present, the prescribing physician confirms that the patient has not previously received Zolgensma.

xi. For a patient currently receiving or who has received prior treatment with Spinraza (nusinersen intrathecal injection), the prescribing physician confirms that further therapy with Spinraza will be discontinued; AND

xii. For a patient currently receiving or who has received prior treatment with Evrysdi (risdiplam oral solution), the prescribing physician confirms that further therapy with Evrysdi will be discontinued; AND

xiii. Medication is prescribed by a physician who has consulted with or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; AND

xiv. If criteria A through M are met, approve one single intravenous infusion of Zolgensma at a dose of 1.1 x 10^{14} vector genomes per kg (vg/kg) based on the current patient weight in kg (within the past 14 days) **[documentation required]**. Zolgensma is provided as a customized kit to meet dosing requirements for each patient per their documented weight (in kilograms). Configuration of the dose kit is based on weight (per the cited NDC) as in Table 2 below.

Table 2. Dose of Zolgensma Based on Availability.[1]
[*] Dose volume is calculated using the upper limit of the patient weight range for pediatric patients less than 2 years of age between 2.6 kg and 21.0 kg.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zolgensma is not recommended in the following situations:

86. Patient has Complete Paralysis of All Limbs. This is cited as a limitation of use in the Zolgensma prescribing information.[1] Data are needed to determine if this patient population would derive benefits from Zolgensma.

87. Patient has Permanent Ventilator Dependence. This is cited as a limitation of use in the Zolgensma prescribing information.[1] Data are needed to determine if this patient population would derive benefits from Zolgensma.

88. Administration to Individuals In Utero. Zolgensma is not approved for in utero administration per the prescribing information.

89. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Spinal Muscular Atrophy – Spinraza Prior Authorization Policy
- Spinraza® (nusinersen intrathecal injection – Biogen)

REVIEW DATE: 11/01/2023

OVERVIEW

Spinraza, a survival motor neuron 2 (SMN2)-directed antisense oligonucleotide, is indicated for the treatment of spinal muscular atrophy in pediatric and adult patients.[1]

Disease Overview

Spinal muscular atrophy is a genetic, autosomal recessive muscular disorder caused by deletion or loss of function mutation in the survival motor neuron 1 (SMN1) gene.[2-5] The reduced levels of survival motor neuron (SMN) protein causes degeneration of lower motor neurons.[5] Although the condition is a multisystem disorder, it is clinically characterized by progressive muscle weakness and atrophy. Patients have difficulties with ambulation, head control, feeding, and respiration. Cognitive development is not impacted. In the US, spinal muscular atrophy affects approximately one in 11,000 infants and has an average carrier frequency of one in 54 individuals; as many as 10,000 to 20,000 children and adults in the US may be impacted.[5] Although the condition can be present in individuals of any age, it is more frequently diagnosed in infants and children, as it is more severe in this population.[2-5] The phenotypic expression of the disease is impacted by the presence of the SMN2 gene copy number. SMN1 is responsible for producing most of the effective SMN protein, although some SMN protein can be made by the SMN2 gene. Therefore, patients with a deletion of the SMN1 gene may have the potential for making some SMN protein through the SMN2 gene copy, although in most cases the resulting protein made by this gene is truncated and is not as effective or functional. Data have shown that patients with a higher number of SMN2 copies generally have a more mild phenotypic disease expression. Gene deletion testing for spinal muscular atrophy can be performed at many diagnostic laboratories. Of note, various motor ability assessments are used in clinical practice to characterize functional impairment in spinal muscular atrophy.[2-5] A variety of functional motor scales are utilized to evaluate patients.[6] Table 1 describes disease types. A different manner of categorization classifies the three most common types as follows: Type 1 patients are "non-sitters", Type 2 patients are "sitters", and Type 3 patients are "walkers".[3,5]

Table 1. Types of Spinal Muscular Atrophy.[2-5]
SMA – Spinal muscular atrophy; SMN2 – Survival motor neuron 2.

Besides Spinraza, other therapies are available. **Evrysdi®** (risdiplam oral solution), a SMN2 splicing modifier, is indicated for the treatment of spinal muscular atrophy in pediatric and adult patients.[7] The primary pivotal data include infantile-onset (Type 1) and later-onset (Type 2 and Type 3) spinal muscular atrophy primarily in children and adults up to 25 years of age. Data are also available in presymptomatic infants who were genetically diagnosed with spinal muscular atrophy.

Zolgensma® (onasemnogene abeparvovec-xioi intravenous infusion), an adeno-associated virus vector-based gene therapy, is indicated for the treatment of pediatric patients < 2 years of age with spinal muscular atrophy with bi-allelic mutations in the SMN1 gene.[8] The agent works by providing a copy of the gene encoding the SMN protein, which increases its production. Zolgensma is administered as a single-dose intravenous infusion over 60 minutes. Pivotal studies mainly involve infants with two or three SMN2 gene copies with primarily Type 1 or Type 2 disease.

Clinical Efficacy

Spinraza was investigated in a pivotal trial called ENDEAR, which was a Phase III, multicenter, multinational, randomized, double-blind, sham-procedure controlled study involving 121 symptomatic infants diagnosed with infantile-onset spinal muscular atrophy (Type I).[1,9] Patients were randomized 2:1 to receive either Spinraza (n = 80) or sham injection (n = 41).[1] Eligible patients were ≤ 7 months of age at the time of the first dose and diagnosed with spinal muscular atrophy with a symptom onset prior to 6 months of age. Baseline demographics were balanced between the Spinraza and control groups with the exception of age at first treatment (median age of 175 and 206 days, respectively).[1] At baseline, all infants were symptomatic, hypotonic and weak, which are features consistent with a phenotype that is most likely to be categorized as spinal muscular atrophy Type 1.[9] Patients had two SMN2 gene copies. The median time of treatment was 261 days (range 6 to 442 days).[1] Those who received Spinraza compared with sham-control experienced improvement on achieving motor milestone responses. Outcomes assessing survival also revealed improvements for patients receiving Spinraza vs. sham control.

CHERISH was a multicenter, double-blind, sham-controlled, Phase III trial which involved children with symptomatic later-onset spinal muscular atrophy who were 2 to 12 years of age (n = 126) with likely Type 2 or 3 disease (symptom onset after 6 months of age).[1,10] Patients were randomized (2:1) to receive Spinraza or sham injection. Three SMN2 gene copies were reported among 88% of patients; approximately 8% of patients had two SMN2 gene copies. The median age at screening was 4 years and 3 years in the Spinraza and sham procedure control groups, respectively.[1,10] Patients who received Spinraza experienced more improvement in motor milestones compared with sham control.

NURTURE was an open-label uncontrolled trial involving patients with presymptomatic spinal muscular atrophy who ranged in age from 3 days to 42 days at the time of the first dose (n = 25).[1,11] Patients were required to have two or three SMN2 gene copies.[11] Some patients who were given Spinraza prior to the onset of symptoms related to spinal muscular atrophy survived without requiring permanent ventilation beyond what would be anticipated based on their SMN2 copy number. Also, some patients also met age-appropriate growth and development motor milestones (e.g., ability to sit unassisted, stand, or walk). Data are available from almost a median of 3-year follow-up.

The EMBRACE trial showed benefits of Spinraza in infants/children with infantile- or later-onset spinal muscular atrophy who were not eligible for the ENDEAR or CHERISH studies.[12] Other data with Spinraza are also available, including an accumulation of data in adults.[13-26] Follow-up is available for up to 4 years. Patients had a slowing of decline, achieved milestones, and experienced additional improvement in scales assessing motor function.

Dosing

Spinraza is given intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures.[1] The recommended dosage is 12 mg (5 mL) per administration. Initiate Spinraza treatment with four loading doses. The first three loading doses should be administered at 14-day intervals. The fourth loading dose should be given 30 days after the third dose. A maintenance dose should be given once every 4 months thereafter. There are additional recommendations in patients who have missed doses. The safety and effectiveness of Spinraza in pediatric patients from newborn to 17 years of age have been established.

Guidelines

The Spinal Muscular Atrophy Newborn Screening Multidisciplinary Working Group is comprised of clinicians and geneticists with expertise in spinal muscular atrophy who developed a treatment algorithm in 2018 for infants who have positive results from a newborn screening test for spinal muscular atrophy.[27] Spinal muscular atrophy Types 1 and 2 comprise a large majority of cases and account for many patients

who screen positively for spinal muscular atrophy with three or fewer SMN2 gene copies. Immediate treatment is recommended in patients with two or three SMN2 gene copies. Treatment recommendations for patients who screen positive for spinal muscular atrophy and have only one SMN2 gene copy is more complicated.[27] In 2020, the Working Group updated recommendations that infants diagnosed with spinal muscular atrophy via newborn screening with four SMN2 gene copies should receive immediate treatment.[28] Also, patients with five (or more) SMN2 gene copies should be observed and screened for symptoms.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Spinraza. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Due to the specialized skills required for evaluation and diagnosis of patients treated with Spinraza, as well as the monitoring required for adverse events and long-term efficacy, approval requires Spinraza to be prescribed by a physician who has consulted with or who specializes in the condition. For certain criteria, verification is required as noted by **[verification in claims history required]**. All reviews will be forwarded to the Medical Director for evaluation.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information. Subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *Spinal Muscular Atrophy – Spinraza Prior Authorization Policy* through the Coverage Review Department, and who is requesting reauthorization, are NOT required to re-submit documentation for reauthorization, except for the criterion requiring documentation of response or benefit to Spinraza therapy.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Spinraza is recommended in those who meet the following criteria:

FDA-Approved Indication

11. Spinal Muscular Atrophy – Treatment. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets all of the following (i, ii, iii, iv, v, and vi):

ii. Baseline motor ability assessment that suggests spinal muscular atrophy (based on age, motor ability, and development) has been performed from one of the following exams (a, b, c, d, e, f, or g) **[documentation required]**:

a) Bayley Scales of Infant and Toddler Development; OR

b) Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND); OR

c) Hammersmith Functional Motor Scale Expanded (HFMSE); OR

d) Hammersmith Infant Neurological Exam Part 2 (HINE-2); OR

e) Motor Function Measure-32 Items (MFM-32); OR

f) Revised Upper Limb Module (RULM) test; OR

g) World Health Organization motor milestone scale; AND

iii. Patient has had a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic pathogenic variants in the survival motor neuron 1 (SMN1) gene **[documentation required]**; AND

Note: Pathogenic variants may include homozygous deletion, compound heterozygous mutation, or a variety of other rare mutations.

iv. Patient meets one of the following (a or b):

a) Patient has two or three survival motor neuron 2 (SMN2) gene copies **[documentation required]**; OR

b) Patient meets both of the following criteria [(1) and (2)]:

(1) Patient has four survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND

(2) Patient has objective signs consistent with spinal muscular atrophy Types 1, 2, or 3 **[documentation required]**; AND

v. For a patient currently receiving or who has received prior treatment with Evrysdi (risdiplam oral solution), the prescribing physician confirms that further therapy with Evrysdi will be discontinued; AND

vi. Patient has not received Zolgensma (onasemnogene abeparvovec-xioi intravenous infusion) in the past **[verification in claims history required]**; AND

Note: Verify through claims history that the patient has not previously received Zolgensma. If no claim for Zolgensma is present, the prescribing physician confirms that the patient has not previously received Zolgensma.

vii. Medication is prescribed by a physician who has consulted with or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; OR

B) Patient Currently Receiving Spinraza Therapy. Approve for one dose (for a dose to be used once within the next 4 months as maintenance therapy) if the patient meets all of the following (i, ii, iii, iv, v, vi, and vii):

i. Patient has had a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic pathogenic variants in the survival motor neuron 1 (SMN1) gene **[documentation required]**; AND

Note: Pathogenic variants may include homozygous deletion, compound heterozygous mutation, or a variety of other rare mutations.

ii. Patient meets one of the following (a or b):

a) Patient has two or three survival motor neuron 2 (SMN2) gene copies **[documentation required]**; OR

b) Patient meets both of the following [(1) and (2)]:

(3) Patient has four survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND

(4) Patient has objective signs consistent with spinal muscular atrophy Types 1, 2, or 3 **[documentation required]**; AND

iii. Four months has elapsed since the last dose; AND

iv. For a patient currently receiving or who has received prior treatment with Evrysdi (risdiplam oral solution), the prescribing physician confirms that further therapy with Evrysdi will be discontinued; AND

v. Patient has not received Zolgensma (onasemnogene abeparvovec-xioi intravenous infusion) in the past **[verification in claims history required]**; AND

Note: Verify through claims that the patient has not previously received Zolgensma. If no claim for Zolgensma is present, the prescribing physician confirms that the patient has not previously received Zolgensma.

vi. Medication is prescribed a physician who has consulted with or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; AND

vii. Patient must meet one of the following (a or b):

a) Patient must have had a positive clinical response (for example, improvement or stabilization) from pretreatment baseline status (i.e., within the past 4 months) with Spinraza from one of the following [(1), (2), (3), (4), (5), (6), or (7)] **[documentation required]**:

(1) Bayley Scales of Infant and Toddler Development; OR

(2) Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND); OR

(3) Hammersmith Functional Motor Scale Expanded (HFMSE); OR

(4) Hammersmith Infant Neurological Exam Part 2 (HINE-2); OR

(5) Motor Function Measure-32 Items (MFM-32); OR

(6) Revised Upper Limb Module (RULM) test; OR

(7) World Health Organization motor milestone scale; OR

b) According to the prescribing physician, the patient has responded to Spinraza and continues to benefit from ongoing Spinraza therapy by the most recent (i.e., within the past 4 months) physician monitoring/assessment tools **[documentation required]**.

Note: Examples include pulmonary function tests showing improvement, bulbar function test results suggest benefits, reduced need for respiratory support, decrease in the frequency of respiratory infections or complications and/or prevention of permanent assisted ventilation.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Spinraza is not recommended in the following situations:

90. Patient has Complete Paralysis of All Limbs. Data are needed to determine if this patient population with advanced spinal muscular atrophy would derive benefits from Spinraza.

91. Patient has Permanent Ventilator Dependence. Data are needed to determine if this patient population with advanced spinal muscular atrophy would derive benefits from Spinraza.

92. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Synagis Prior Authorization Policy
- Synagis® (palivizumab intramuscular injection – Sobi)

REVIEW DATE: 08/16/2023

OVERVIEW

Synagis, a respiratory syncytial virus (RSV) F protein inhibitor monoclonal antibody, is indicated for the **prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease**.[1] Safety and efficacy were established in children with bronchopulmonary dysplasia, infants with a of premature birth, and children with hemodynamically significant congenital heart disease.

The safety and efficacy of Synagis for the treatment of RSV have not been established.[1] The recommended dose is 15 mg/kg intramuscularly once monthly (every 30 days). The first dose of Synagis should be administered prior to commencement of the RSV season and the remaining doses should be administered monthly throughout the RSV season.

RSV Seasonality

The Centers for Disease Control and Prevention National Respiratory and Enteric Virus Surveillance System provides reports determining RSV seasonality, nationally and by region. The COVID-19 pandemic disrupted RSV seasonality from 2020 to 2022.[2] To describe US RSV seasonality during pre-pandemic and pandemic periods, polymerase chain reaction (PCR) test results reported to the National Respiratory and Enteric Virus Surveillance System during July 2017 through February 2023 were analyzed. Seasonal RSV epidemics were defined as the weeks during which ≥ 3% of PCR test results were positive for RSV. Nationally, pre-pandemic seasons (2017 to 2020) began in October, peaked in December, and ended in April. During 2020/2021, the typical winter RSV epidemic did not occur. The 2021/2022 season began in May, peaked in July, and ended in January. The 2022/2023 season started (June) and peaked (November) later than the 2021/2022 season, but earlier than pre-pandemic seasons. In both pre-pandemic and pandemic periods, epidemics began earlier in Florida and the southeast and later in regions further north and west. Although the timing of the 2022/2023 season suggests that seasonal patterns are returning toward those observed in pre-pandemic years, off-season RSV circulation may continue.

During the 2022/2023 surveillance year, onset occurred in June, the proportion of positive PCR results peaked in November, and the peak was higher (19%) than that during pre-pandemic seasons (range 13% to 16%). The epidemic lasted 32 weeks until the offset occurred in January.

Guidelines

The American Academy of Pediatrics (AAP) Policy Statement on the Updated Guidance for Synagis Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for RSV Infection was updated on August 1, 2014.[3] Additionally, the AAP Red Book was updated in 2021.[4] The AAP Red Book provides eligibility criteria for prophylaxis of high-risk infants and children in the following situations: preterm infants with chronic lung disease, infants with congenital heart disease (including those who undergo cardiac transplantation during the RSV season), preterm infants (before 29 weeks, 0 days' gestation) without chronic lung disease or congenital heart disease, children with anatomic pulmonary abnormalities or neuromuscular disorders, and immunocompromised children. Data are insufficient to justify a recommendation for routine use of prophylaxis in patients with Down syndrome or among those with cystic fibrosis, unless other indications are present.

The Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) [August 25, 2023] recommend one dose of Beyfortus (nirsevimab-alip intramuscular injection) for all infants < 8 months of age born during or entering their first RSV season (50 mg for infants < 5 kg and 100 mg for infants ≥ 5 kg).[11] ACIP recommends one dose of Beyfortus (200 mg, administered as two 100-mg injections given at the same time at different injection sites) for infants and children 8 to 19 months of age who are at increased risk for severe RSV disease and entering their second RSV season.

The ACIP and AAP have published considerations for the 2023/2024 RSV season with regard to Synagis vs. Beyfortus in high-risk infants (August 15, 2023).[13] In general, the joint recommendations mirror the ACIP recommendations above. In addition, if Beyfortus is administered, Synagis should not be administered later that season. If Synagis was initially administered for the season, and < 5 doses were administered, the infant should receive one dose of Beyfortus. No further Synagis should be administered. If Synagis was administered in the first RSV season, and the child is eligible for RSV prophylaxis in the second RSV season, the child should receive Beyfortus in the second RSV season, if available. An additional recommendation regarding Beyfortus is that in healthy infants born at the end of their first RSV season, who did not receive Beyfortus and are < 8 months of age entering their second RSV season, a single dose of Beyfortus may be given.

On October 23, 2023, the CDC issued a Health Alert Network Health Advisory to provide options for clinicians to protect infants from RSV in the context of a limited supply of Beyfortus.[14] In the context of limited supply during the 2023/2024 RSV season, CDC recommends prioritizing available Beyfortus 100 mg doses for infants at the highest risk for severe RSV disease: young infants (< 6 months of age) and infants with underlying conditions that place them at highest risk for severe RSV disease. Recommendations for using 50 mg doses remain unchanged at this time. The CDC further recommends that providers suspend using Beyfortus in Synagis-eligible children who are 8 to 19 months of age for the 2023/2024 RSV season. These children should receive Synagis according to the AAP recommendations. Beyfortus should continue to be offered to American Indian and Alaska Native children aged 8 to 19 months who are not Synagis-eligible and who live in remote regions, where transporting children with severe RSV for escalation of medical care is more challenging or in communities with known high rates of RSV among older infants and toddlers.

RSV Seasonality and Recommendations

Although typical RSV seasonality in the US occurs primarily in the fall and winter months, there was a rapid decrease in RSV infections in the US beginning in March 2020 following non-pharmacologic interventions to prevent COVID-19.[6] RSV activity remained very low through the traditional 2020-2021 fall-winter season but began to increase in spring 2021 and cases rose to a level similar to a fall-winter season throughout the US over the summer and fall of 2021.[7] This was a deviation from usual RSV epidemiology.[6,7] Because of the change in RSV circulation, AAP strongly supported consideration for use of Synagis in eligible patients during the interseasonal spread of RSV.[6] According to a statement released by AAP on December 17, 2021, the 2021-2022 winter RSV season is considered a new season, rather than a continuation of the interseason spread in the spring and summer of 2021.

As of July 2022, RSV activity in the US remains variable by region but is increasing in some parts of the country.[7] Due to the shift in RSV seasonality noted in 2021 and the current regional rise in interseason RSV cases, the AAP continues to support the use of Synagis in eligible infants in any region experiencing rates of RSV activity at any time in 2022 similar to a typical fall-winter season. The standard administration of Synagis, 5 consecutive monthly doses, is recommended by the AAP to provide serum levels associated with protection for 6 months, the length of a typical RSV season. The AAP will continue to monitor the interseasonal trends and update this guidance as needed if the RSV season extends longer than 6 months.

The start of the RSV season has historically been defined as case positivity rate of 10% by antigen or PCR testing.[8] However, a 10% threshold for PCR tests has been found to be imprecise for characterizing the RSV season. Therefore, other thresholds have been used for PCR tests. A 3% threshold has been found to be a simple method to assess the onset and offset of the RSV season (defining the RSV season onset as the first of 2 consecutive weeks when the weekly percentage of positive tests for RSV is > 3% and season offset as the last week that the percentage of positive tests is >3%).[8,9] A 10% threshold appears reasonable for antigen testing.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Synagis. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because five monthly doses of Synagis at 15 mg/kg per dose will provide more than 6 months of serum Synagis concentrations for most infants, administration of more than five monthly doses is not recommended within the continental US. Children who qualify for five monthly doses of Synagis should receive the first dose at the time of onset of the RSV season. For qualifying infants born during the RSV season, fewer than five monthly doses will be needed to provide protection until the RSV season ends in their region (maximum of five monthly doses). For the purposes of this policy, RSV season onset is defined as the first 2 consecutive weeks when the percentage of positive tests for RSV is > 3% by PCR or > 10% by antigen testing. RSV season offset is defined as the last week that the percentage of positive tests for RSV is > 3% by PCR of > 10% by antigen testing.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Synagis is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Chronic Lung Disease**. Approve for a maximum of 5 months during the RSV season if the patient meets one of the following (A or B):
    - **a)** Patient is < 12 months of age at the start of the RSV season and meets the following (i and ii):
        - **a)** Patient was born at < 32 weeks, 0 days gestation; AND
        - **b)** Patient required > 21% oxygen for at least 28 days after birth; OR
    - **b)** Patient is ≥ 12 months of age but < 24 months of age at the start of the RSV season and meets the following (i, ii, and iii):
        - **a)** Patient was born at < 32 weeks, 0 days gestation; AND
        - **b)** Patient required > 21% oxygen for at least 28 days after birth; AND
        - **c)** Patient has required medical therapy (i.e., supplemental oxygen, diuretic therapy, or chronic corticosteroid therapy) during the 6 months before the start of the second RSV season.

2. **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Congenital Heart Disease.** Approve for a maximum of 5 months during the RSV season if the patient meets the following (A, B, and C):

a) Patient is < 12 months of age at the start of the RSV season; AND
b) According to the prescriber, patient meets one of the following (i, ii, iii, or iv):
i. Patient is considered to have hemodynamically significant cyanotic congenital heart disease; OR
ii. Patient meets all of the following (a, b, and c):
1. Patient has acyanotic heart disease; AND
2. Patient is receiving medication to control heart failure; AND
3. Patient will require cardiac surgical procedures; OR
iii. Patient has moderate to severe pulmonary hypertension; OR
iv. Patient meets both of the following (a and b):
1. Patient has lesions that have been adequately corrected by surgery; AND
2. Patient continues to require medication for congestive heart failure; AND
c) Synagis is prescribed by or in consultation with a cardiologist or intensivist.

3. **Respiratory Syncytial Virus (RSV), Prevention in a Patient Born Prematurely.** Approve for a maximum of 5 months during the RSV season if the patient meets the following (A and B):
A) Patient is < 12 months of age at the start of the RSV season; AND
B) Patient was born before 29 weeks, 0 days gestation (≤ 28 weeks, 6 days gestation).

Other Uses with Supportive Evidence

4. **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Anatomic Pulmonary Abnormalities or a Neuromuscular Disorder.** Approve for a maximum of 5 months during the RSV season if the patient meets the following (A and B):
A) Patient is < 12 months of age at the start of the RSV season; AND
B) According to the prescriber, the patient's condition compromises the handling of respiratory secretions.

5. **Respiratory Syncytial Virus (RSV), Prevention in an Immunocompromised Patient.** Approve for a maximum of 5 months during the RSV season if the patient meets the following (A, B, and C):
Note: Examples of immunocompromised patients include those receiving chemotherapy and those with hematopoietic stem cell transplant or solid organ transplant.
a) Patient is < 24 months of age at the start of the RSV season; AND
b) According to the prescriber, the patient is/will be profoundly immunocompromised during the RSV season; AND
c) Synagis is prescribed by or in consultation with an immunologist or an infectious diseases specialist.

D) 6. Respiratory Syncytial Virus (RSV), Prevention in a Patient with Cardiac Transplant. Approve for a maximum of 5 months during the RSV season if the patient meets the following (A, B, and C):
E) Note: A patient with cardiac transplant may also be immunocompromised. In a patient who does not meet criteria for cardiac transplant below, please see criterion 5 above (Respiratory Syncytial Virus [RSV], Prevention in an Immunocompromised Patient).
a) Patient is < 24 months of age at the start of the RSV season; AND
b) Patient has undergone or will undergo cardiac transplantation during the current RSV season; AND

c) Synagis is prescribed by or in consultation with a cardiologist, intensivist, or transplant physician.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Synagis is not recommended in the following situations:

1. **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Cystic Fibrosis Who Does Not Meet Any of the Approval Criteria.** The AAP guidelines for RSV note that routine use of Synagis prophylaxis in patients with cystic fibrosis, including neonates diagnosed with cystic fibrosis by newborn screening, is not recommended unless other indications are present.[4] Available studies indicate the incidence of RSV hospitalization in children with cystic fibrosis is uncommon and unlikely to be different from children without cystic fibrosis.[3] A Cochrane Review identified one trial (presented in poster/abstract form) eligible for their review of Synagis prophylaxis in children with cystic fibrosis.[5] In this prospective, double-blind, placebo-controlled, multi-center study, 14.1% vs. 14.9% of Synagis and placebo-treated patients, respectively were hospitalized within the first 6 months, and only one patient in each group was identified with RSV infection. There were no deaths in either group of patients during the first 6 months follow-up; this outcome was not reported at 12 months follow-up.

2. **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Down Syndrome Who Does Not Meet Any of the Approval Criteria.** Data suggest that children with Down syndrome have a slightly higher hospitalization rate for RSV, but the absolute number of hospitalizations is small, and a number of children with Down syndrome are at increased risk because of other qualifying risk factors (e.g., congenital heart disease, abnormalities of the respiratory tract, muscle dystonia).[3]

3. **Respiratory Syncytial Virus (RSV), Treatment of Disease.** There are limited data investigating Synagis for the treatment of established RSV infections. Passive antibody administration is not effective in treatment of RSV disease and is not approved or recommended for this indication.[3,4] If any infant or young child receiving monthly Synagis prophylaxis experiences a breakthrough RSV hospitalization, monthly prophylaxis should be discontinued because of the extremely low likelihood of a second RSV hospitalization (< 0.5%).[4]

4. **Use in a Patient who has Received Beyfortus (nirsevimab-alip intramuscular injection) in the Same RSV Season.** Synagis should not be administered to infants who have already received Beyfortus for the same RSV season.[10,11,12] However, if Synagis was initially administered for the season, and < 5 doses were administered, the infant should receive one dose of Beyfortus.[12] No further Synagis should be administered. If Synagis was administered in the first RSV season, and the child is eligible for RSV prophylaxis in the second RSV season, the child should receive Beyfortus in the second RSV season, if available. Note: The RSV season is generally 6 months in duration.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Tasimelteon Products Prior Authorization Policy
- Hetlioz™ (tasimelteon capsules – Vanda, generic)
- Hetlioz LQ™ (tasimelteon oral suspension – Vanda)

REVIEW DATE: 01/18/2023

OVERVIEW

Tasimelteon products are melatonin receptor agonists indicated for the following uses:[1,2]

- Tasimelteon capsule is indicated for the treatment of:
  - **Non-24-Hour Sleep-Wake Disorder** (Non-24).
  - **Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS)**, in patients ≥ 16 years of age.
- Hetlioz LQ is indicated for the treatment of **nighttime sleep disturbances in SMS**, in patients 3 to 15 years of age.

Disease Overview

Non-24 is a chronic circadian rhythm disorder that is due to the misalignment of the endogenous master body clock to the 24-hour day which disrupts the sleep-wake cycle and commonly is thought to be caused by the failure of light to reach the suprachiasmatic nuclei. Patients who are completely blind are particularly susceptible to this condition; as many as one-half to three-quarters of totally blind patients have Non-24, which is approximately 65,000 to 95,000 Americans.[3-8] Patients can be diagnosed using circadian phase markers (e.g., measurement of urinary melatonin levels, dim light melatonin onset [assessed in blood or saliva], or assessing core body temperature).[3,8,9] Alternative forms of diagnosis include actigraphy and assessment of sleep logs (sleep diaries).[3,8,9] Actigraphy is a non-invasive method of monitoring human rest and activity cycles and involves the use of a portable device to document movement. Other reviews confirm these diagnostic methods.[8,9]

SMS is a rare disorder identified by an array of physical, neurobehavioral, and developmental characteristics.[15] In the United States, the incidence is estimated to be 1 in 15,000 to 25,000 people in the general population. Cases of SMS are predominantly related to either a deletion or mutation in the *RAI1* gene. Sleep disturbances start as early as one year of age and continue into adulthood and include shortened sleep cycles with multiple awakenings during the night, early morning arousal from sleep, and increased somnolence during daytime hours. Inability to achieve a normal sleeping pattern appears to aggravate behavioral issues such as impulsivity, aggression, hyperactivity and frequent temper tantrums. Sleep issues in SMS have been attributed to a primary disturbance of the circadian clock disruption and instabilities in melatonin secretion. Physical traits such as muscle weakness, obesity-related breathing difficulties, and facial composition can be underlying factors that affect sleep.

Clinical Efficacy

The efficacy of Hetlioz for Non-24 was established in two Phase III pivotal studies involving totally blind patients who reported no light perception with Non-24 for up to 6 months and evaluated the effects of Hetlioz withdrawal.[1,3] In the Hetlioz group, 29% of patients (n = 12) met responder criteria, defined as patients with both a ≥ 45 minute increase in nighttime sleep and a ≥ 45 minute decrease in daytime nap time, compared with 12% of patients (n = 5) who received placebo (time of endpoint assessment not stated).[1] During the withdrawal period of the trial, which lasted 8 weeks, 90% of patients who continued

Hetlioz (n = 9/10) remained entrained (circadian rhythm synchronized to 24-hour day) compared with 20% of patients randomized to receive placebo (n = 2/10).[3,4]

The data of Hetlioz and Hetlioz LQ supporting benefits for nighttime sleep disturbances in SMS are underwhelming.[1,17] The pivotal trial for SMS included very few patients and was relatively short-term; this condition would likely require long-term therapy. Only one of the two primary efficacy endpoints was statistically significant after controlling for multiple comparisons.

Guidelines

In 2015, clinical practice guidelines were published by the American Academy of Sleep Medicine that address Non-24.[6] The condition mainly occurs in patients who are blind. The Task Force states that there is no evidence to support the use of sleep-promoting medications in patients with Non-24. Data suggest that melatonin entrainment occurs with melatonin at a greater rate than placebo and melatonin can be an effective treatment for Non-24. The Task Force recommendation was that clinicians use strategically timed melatonin for the treatment of Non-24 in adults who are blind (versus no treatment). There are insufficient data to support use of melatonin among sighted patients with Non-24 (versus no treatment).

The Parents and Researchers Interested in SMS (PRISMS) created medical management guidelines for the diagnosis, treatment of manifestations, and ongoing surveillance of SMS.[16] The guidelines do not address Hetlioz/Hetlioz LQ. Multidisciplinary treatment is recommended. The guidelines recognize sleep management is a challenge and no well controlled treatment trials have been reported. The first suggestion is to incorporate a good sleep routine (e.g., consistent bedtime and bedtime routine, quiet/non-stimulating activities, use of white noise or a rhythmic sound, and a comfortably cool/dark room). Concerns for sleep apnea should be addressed. Melatonin is endorsed as monotherapy for sleep management. The concomitant use of a morning beta-blocker (acebutolol) with an evening dose of melatonin for 6 to 8 weeks could be beneficial to restore circadian plasma melatonin rhythmicity, decrease daytime sleepiness, improve daytime behavior, and enhance sleep in children with SMS.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of tasimelteon capsules. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with tasimelteon capsules as well as the monitoring required for adverse events and long-term efficacy, approval requires tasimelteon capsules to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Due to insufficient clinical efficacy data for its FDA-approved use, **approval is not recommended** for Hetlioz LQ.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of tasimelteon capsule is recommended in those who meet the following criteria:

FDA-Approved Indication

12. Non-24-Hour Sleep-Wake Disorder (Non-24). Approve for the duration noted if the patient meets one of the following conditions (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets all of the following criteria (i, ii, iii, iv, and v):

i. Patient is ≥ 18 years of age; AND

ii. Patient is totally blind with no perception of light; AND

iii. Diagnosis of Non-24 is confirmed by meeting ONE of the following conditions (a or b):

a) Assessment of at least one physiologic circadian phase marker; OR

Note: Examples of physiologic circadian phase markers include measurement of urinary melatonin levels, dim light melatonin onset (as measured in blood or saliva), and assessment of core body temperature.

b) If assessment of at least one physiologic circadian phase marker cannot be done, the diagnosis must be confirmed by actigraphy performed for ≥ 1 week plus evaluation of sleep logs recorded for ≥ 1 month; AND

iv. Patient meets BOTH of the conditions (a and b):

a) Patient has received at least 6 months of continuous therapy (i.e., 6 consecutive months of daily treatment) with melatonin under the guidance of a physician who specializes in the treatment of sleep disorders; AND

b) Patient had inadequate efficacy with melatonin therapy according to the prescriber; AND

Note: Examples of efficacy with melatonin therapy include entrainment, clinically meaningful or significant increases in nighttime sleep, and clinically meaningful or significant decreases in daytime sleep.

v. The medication is prescribed by, or in consultation with, a physician who specializes in the treatment of sleep disorders.

B) Patient is Currently Receiving Tasimelteon Capsules. Approve for 1 year if the patient meets all of the following criteria (i, ii, iii, iv, v, and vi):

i. Patient is ≥ 18 years of age; AND

ii. Patient is totally blind with no perception of light; AND

iii. Patient meets both of the following conditions (a and b):

a) Patient has received at least 6 months of continuous therapy (i.e., 6 consecutive months of daily treatment) with melatonin under the guidance of a physician who specializes in the treatment sleep disorders; AND

b) Patient had inadequate efficacy with melatonin therapy according to the prescriber; AND

Note: Examples of efficacy with melatonin therapy include entrainment, clinically meaningful or significant increases in nighttime sleep, and clinically meaningful or significant decreases in daytime sleep.

iv. Patient meets both of the following conditions (a and b):

a) Patient has received at least 6 months of continuous therapy (i.e., 6 consecutive months of daily treatment) with tasimelteon capsules under the guidance of a physician who specializes in the treatment of sleep disorders; AND

Note: A patient who has not received at least 6 months of continuous tasimelteon capsules therapy, or if the therapy has not been continuous (i.e., 6 consecutive months of daily treatment), should follow criterion 1 (initial therapy).

b) Patient has achieved adequate results with tasimelteon capsules therapy according to the prescriber; AND

Note: Examples of adequate results with tasimelteon capsules therapy include entrainment, clinically meaningful or significant increases in nighttime sleep, clinically meaningful or significant decreases in daytime sleep.

v. The medication is prescribed by, or in consultation with, a physician who specializes in the treatment of sleep disorders.

II. Coverage of Hetlioz LQ is not recommended.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of tasimelteon /Hetlioz LQ is not recommended in the following situations:

104. Insomnia, Primary. Many other agents are available.[10] Only limited data have investigated use of Hetlioz in patients with primary insomnia.[10] Further data are needed to establish the safety and efficacy of Hetlioz.

105. Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS). Efficacy data for Hetlioz/Hetlioz LQ supporting benefits for nighttime sleep disturbances in SMS are underwhelming.[1,17]

106. Ramelteon Tablets (Rozerem™, generic), Concomitant Therapy. Ramelteon, a melatonin receptor agonist, is indicated for the treatment of insomnia characterized by difficulty with sleep onset.[12] The safety and efficacy of concomitant use of ramelteon tablets and Hetlioz have not been studied and it is suspected that the adverse events with use of these agents with a similar mechanism of action taken together may be additive (e.g., central nervous system effects [somnolence], hepatic impairment). Ramelteon has not been studied in Non-24. In the clinical trials with Hetlioz, patients were not permitted to use medications that could interfere with the assessment of circadian rhythms.

107. Sedative Hypnotic Medications or Other Medications for Insomnia or Other Sleep-Related Disorders, Concomitant Therapy (e.g., benzodiazepines [triazolam, temazepam], nonbenzodiazepine hypnotics [e.g., zolpidem, zaleplon], chloral hydrate). There are no data to support the safety and efficacy of hypnotic medications in patients with Non-24.[6] Also, there are no data to determine the safety and efficacy of Hetlioz when used with other sedative hypnotic medications or other medications for insomnia or sleep-related disorders.[13]

108. Sleep-Related Disorders, Other Types (e.g. shift work disorder, jet lag disorder, advanced sleep phase disorder, delayed sleep phase disorder, irregular sleep-wake rhythm disorder). A published investigation details a Phase II study (n = 29) and a Phase III study (n = 411) assessing Hetlioz treatment in adults with transient insomnia associated with shifted sleep and wake time.[14] Further studies are needed to establish the efficacy and safety of Hetlioz in patients with other types of sleep-related disorders.

109. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Testosterone (Oral, Topical, and Nasal) Products Prior Authorization Policy

Oral Testosterone Products

- Jatenzo® (testosterone undecanoate capsules – Clarus/Tolmar)
- Kyzatrex™ (testosterone undecanoate capsules – Marius)
- Tlando® (testosterone undecanoate capsules – Antares)

Transdermal Patch

- Androderm® (testosterone transdermal system [2,4 mg/day] – Allergan)

Transdermal Gels

- AndroGel® (testosterone 1% gel (generics only), 1.62% gel – AbbVie, generic)
- Fortesta™ (testosterone 2% gel – Endo, generic)
- Testim® (testosterone 1% gel – Endo, generic)
- Vogelxo™ (testosterone 1% gel – Upsher-Smith, generic)

Transdermal Solution

- testosterone 2% solution – Actavis, generics only

Nasal Gel

- Natesto™ (testosterone nasal gel – Acerus)

REVIEW DATE: 11/08/2023

OVERVIEW

The oral, topical, and nasal testosterone replacement products are all indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.[1-10,15] The labels for the FDA-approved products define those patients and/or conditions for which use of testosterone replacement products is indicated:

- **Primary hypogonadism (congenital or acquired):** testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and above-normal gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]).
- **Hypogonadotropic hypogonadism (congenital or acquired):** gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low serum testosterone concentrations, but have gonadotropins in the normal or low range.

The diagnosis of male hypogonadism is based on both signs/symptoms and low testosterone levels. By restoring normal levels of testosterone, the replacement regimens correct symptoms of hypogonadism, which can include malaise, loss of muscle strength, depressed mood, and decreased libido.[12]

All of the oral, topical, and nasal testosterone replacement product labeling states that due to the lack of controlled evaluations in women and potential virilizing effects, the products are not indicated for use in women.[1-10,15]

Guidelines

- **Hypogonadism:** Guidelines from the American Urological Association (2018) note that clinicians should use a total testosterone level below 300 ng/dL as a reasonable cutoff in support of the diagnosis of low testosterone.[13] A clinical diagnosis requires low testosterone levels (two separate levels, both conducted in the early morning) combined with signs and symptoms. The Endocrine Society guidelines on testosterone therapy in men with hypogonadism (2018) recommend diagnosing hypogonadism in men with symptoms and signs of testosterone deficiency and unequivocally and consistently low serum total testosterone and/or free testosterone concentrations (when indicated).[11]
- **Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Female-To-Male (FTM) Gender Reassignment (i.e., Endocrinologic Masculinization):** A clinical practice guideline published by the Endocrine Society (2017) recommends that, prior to initiation of hormonal therapy, the treating endocrinologist should confirm the diagnostic criteria of gender dysphoria/gender incongruence and the criteria for the endocrine phase of gender transition.[14] The clinician should also evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment. Guidelines mention that clinicians can use either parenteral or transdermal preparations to achieve appropriate testosterone values.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of oral, topical, and nasal testosterone products. In the approval indications, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: males are defined as individuals with the biological traits of a male, regardless of the individuals' gender identity or gender expression. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of some patients treated with testosterone, certain approval conditions require testosterone to be prescribed by or in consultation with a physician who specializes in the conditions being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of oral, topical, and nasal testosterone products is recommended in those who meet one of the following criteria:

FDA-Approved Indication

11. Hypogonadism (Primary or Secondary) in Males* [Testicular Hypofunction/Low Testosterone with Symptoms]. Approve for 1 year if the patient meets the following (A or B):
Note: The pretreatment timeframe refers to signs and symptoms of androgen deficiency and serum testosterone levels prior to the initiation of any testosterone therapy.

A) Initial Therapy. Patient with hypogonadism as confirmed by the following (i, ii, and iii):
- **i.** Patient has had persistent signs and symptoms of androgen deficiency (pretreatment); AND
  Note: Signs and symptoms of androgen deficiency include depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, and loss of libido.
- **ii.** Patient has had two pretreatment serum testosterone (total or bioavailable) measurements, each taken in the morning, on two separate days; AND
- **iii.** The two serum testosterone levels are both low, as defined by the normal laboratory reference values.

B) Patient is Currently Receiving Testosterone Therapy. Approve if the patient meets the following (i and ii):

- **i.** Patient has had persistent signs and symptoms of androgen deficiency (pretreatment); AND
  Note: Signs and symptoms of androgen deficiency include depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, and loss of libido.
- **ii.** Patient has had at least one pretreatment serum testosterone (total or bioavailable) level, which was low, as defined by the normal laboratory reference values.

*Refer to the Policy Statement.

Other Uses with Supportive Evidence

12. Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Female-To-Male (FTM) Gender Reassignment (i.e., Endocrinologic Masculinization). Approve for 1 year if prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of transgender patients.
Note: For a patient who has undergone gender reassignment, use this FTM criterion for hypogonadism indication.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of oral, topical, and nasal testosterone products is not recommended in the following situations:

93. To Enhance Athletic Performance. Topical testosterone products are not recommended for approval because this indication is excluded from coverage in a typical pharmacy benefit.

94. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Testosterone (Injectable) Products Prior Authorization Policy
- Depo®-Testosterone (testosterone cypionate intramuscular injection – Pfizer, generics)
- testosterone enanthate intramuscular injection – Hikma, generic only
- Aveed™ (testosterone undecanoate intramuscular injection – Endo)
- Testopel® (testosterone subcutaneous pellet – Endo)
- Xyosted™ (testosterone enanthate subcutaneous injection – Antares)

REVIEW DATE: 09/06/2023

OVERVIEW

Testosterone regimens can be administered orally, parenterally, or transdermally. All of the injectable agents are indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.[1-5] The prescribing information define these patients and/or conditions for which use of testosterone replacement products are indicated:

- **Primary hypogonadism (congenital or acquired),** for testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchiectomy.
- **Hypogonadotropic hypogonadism (congenital or acquired),** for gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation.

The diagnosis of male hypogonadism is based on both signs/symptoms and low testosterone levels. By restoring normal levels of testosterone, the replacement regimens correct symptoms of hypogonadism, which can include malaise, loss of muscle strength, depressed mood, and decreased libido.[6]

Testopel and testosterone enanthate are also indicated for **delayed puberty**.[2,3] Testosterone enanthate (per the product labeling) may also be used secondarily in **advanced inoperable metastatic mammary cancer** in women who are 1 to 5 years postmenopausal.[2] The goal of therapy is ablation of ovaries. Per labeling, it also can be used in premenopausal women with breast cancer who have benefited from oophorectomy and are considered to have hormone-responsive tumors.

Guidelines

- **Hypogonadism:** Guidelines from the American Urological Association (2018) note that clinicians should use a total testosterone level below 300 ng/dL as a reasonable cut-off in support of the diagnosis of low testosterone.[7] The guidelines additionally note that a diagnosis of low testosterone should be made only after two total testosterone measurements are taken on separate occasions with both conducted in an early morning fashion and that a clinical diagnosis should be made when patients have low testosterone levels combined with signs and symptoms. The Endocrine Society guidelines on testosterone therapy in men with hypogonadism (2018) recommend diagnosing hypogonadism in men with symptoms and signs of testosterone deficiency and unequivocally and consistently low serum total testosterone and/or free testosterone concentrations (when indicated).[8]
- **Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Female-To-Male (FTM) Gender Reassignment (i.e., Endocrinologic Masculinization):** A clinical practice guideline published by the Endocrine Society (2017) recommends that, prior to initiation of hormonal therapy, the treating endocrinologist should confirm the diagnostic criteria of gender dysphoria/gender incongruence and the criteria for the endocrine phase of gender transition.[9] The clinician should also evaluate and address medical conditions that can be exacerbated by hormone

depletion and treatment with sex hormones of the affirmed gender before beginning treatment. Guidelines mention that clinicians can use either parenteral or transdermal preparations to achieve appropriate testosterone levelsvalues.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of injectable testosterone. All approvals are provided for the duration noted below. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: males are defined as individuals with the biological traits of a male, regardless of the individual's gender identity or gender expression; females are defined as individuals with the biological traits of a female, regardless of the individual's gender identity or gender expression. Because of the specialized skills required for evaluation and diagnosis of some patients treated with testosterone, certain approval requires testosterone to be prescribed by or in consultation with a physician who specializes in the conditions being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of injectable testosterone is recommended in those who meet one of the following criteria:

FDA-Approved Indications

13. **Hypogonadism (Primary or Secondary) in Males* [Testicular Hypofunction/Low Testosterone with Symptoms].** Approve for 1 year if the patient meets the following (A or B):
    Note: The pre-treatment timeframe refers to sign and symptoms of androgen deficiency and serum testosterone levels prior to the initiation of any testosterone therapy.
    - **A)** Initial Therapy. Approve in a patient with hypogonadism as confirmed by the following (i, ii, and iii):
        - **i.** Patient has had persistent signs and symptoms of androgen deficiency (pre-treatment); AND
          Note: Signs and symptoms of androgen deficiency include depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, and loss of libido.
        - **ii.** Patient has had two pre-treatment serum testosterone (total or bioavailable) measurements, each taken in the morning, on two separate days; AND
        - **iii.** The two serum testosterone levels are both low, as defined by the normal laboratory reference values.
    - **B)** Patient Currently Receiving Testosterone Therapy. Approve if the patient meets the following (i and ii):
        - **i.** Patient has had persistent signs and symptoms of androgen deficiency (pre-treatment); AND
          Note: Signs and symptoms of androgen deficiency include depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, and loss of libido.
        - **ii.** Patient has had at least one pre-treatment serum testosterone (total or bioavailable) level, which was low, as defined by the normal laboratory reference values.

    * Refer to the Policy Statement

14. **Delayed Puberty or Induction of Puberty in Males* 14 years of Age or Older.** Approve Depo-Testosterone (testosterone cypionate intramuscular injection, generics), testosterone enanthate intramuscular injection, or Testopel for 6 months.

*Refer to the Policy Statement

15. Breast Cancer in Females*. Approve testosterone enanthate intramuscular injection for 6 months if prescribed by or in consultation with an oncologist.

*Refer to the Policy Statement.

Other Uses with Supportive Evidence

16. Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Female-to-Male (FTM) Gender Reassignment (i.e., Endocrinologic Masculinization). Approve for 1 year if prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of transgender patients.
Note: For a patient who has undergone gender reassignment, use this FTM criterion for hypogonadism indication.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of injectable testosterone is not recommended in the following situations:

95. To Enhance Athletic Performance. Injectable testosterone products are not recommended for approval because this indication is excluded from coverage in a typical pharmacy benefit.

96. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Thrombocytopenia – Doptelet Prior Authorization Policy
- Doptelet® (avatrombopag tablets – Dova/AkaRx)

REVIEW DATE: 04/12/2023

OVERVIEW

Doptelet, a thrombopoietin receptor agonist, is indicated for the following uses:[1]

- **Immune thrombocytopenia (ITP)**, chronic for treatment in adults who have had an insufficient response to a previous treatment.
- **Thrombocytopenia,** as treatment in adults with **chronic liver disease** who are scheduled to undergo a procedure.

For chronic ITP, Doptelet should be discontinued if the platelet count does not increase to $\geq 50 \times 10^9$/L within 4 weeks at the maximum dose of 40 mg once daily. The safety and efficacy of Doptelet have not been established in pediatric patients. For chronic liver disease in patients undergoing a procedure, Doptelet is given as a 5-day course beginning 10 to 13 days before the scheduled procedure. In general, patients in the pivotal studies had a platelet count $< 50 \times 10^9$/L.

Guidelines

In 2019, the American Society of Hematology updated guidelines for ITP.[4] Doptelet is not addressed specifically, but there are several recommendations. For adults with ITP for at least 3 months who are corticosteroid-dependent or unresponsive to corticosteroid, a thrombopoietin receptor agonist (either Promacta® [eltrombopag tablets and oral suspension] or Nplate® [romiplostim subcutaneous injection]) or a splenectomy are recommended. In children with newly diagnosed ITP who have non-life-threatening mucosal bleeding, corticosteroids are recommended. For children who have non-life-threatening mucosal bleeding and did not respond to first-line treatment, thrombopoietin receptor agonists are recommended. Other treatment options in children and adults include intravenous immunoglobulin, anti-D immunoglobulin, and rituximab.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Doptelet. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Doptelet as well as the monitoring required for adverse events and long-term efficacy, approval may require Doptelet to be prescribed by or in consultation with a physician who specializes in the condition being treated in certain indications.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Doptelet is recommended in those who meet one of the following criteria:

FDA-Approved Indications

13. Chronic Immune Thrombocytopenia. Approve if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets all of the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets one of the following criteria (a or b):

a) Patient has a platelet count < 30 x 10^9/L (< 30,000/mcL); OR

b) Patient meets both of the following criteria [(1) and (2)]:

(1) Patient has a platelet count < 50 x 10^9/L (< 50,000/mcL); AND

(2) According to the prescriber, the patient is at an increased risk of bleeding; AND

iii. Patient meets one of the following criteria (a or b):

a) Patient has tried at least one other therapy; OR

Note: Examples of therapies are systemic corticosteroids, intravenous immunoglobulin, anti-D immunoglobulin, Promacta (eltrombopag tablets and oral suspension), Nplate (romiplostim subcutaneous injection), Tavalisse (fostamatinib tablets), and rituximab.

b) Patient has undergone splenectomy; AND

iv. The medication is prescribed by or in consultation with a hematologist; OR

B) Patient is Currently Receiving Doptelet. Approve for 1 year if the patient meets both of the following criteria: (i and ii):

i. According to the prescriber, the patient demonstrates a beneficial clinical response; AND

Note: A beneficial response can include increased platelet counts, maintenance of platelet counts, and/or a decreased frequency of bleeding episodes.

ii. Patient remains at risk for bleeding complications.

14. Thrombocytopenia in a Patient with Chronic Liver Disease. Approve for 5 days if the patient meets the following criteria (A, B, and C):

G) Patient is ≥ 18 years of age; AND

H) Patient has a current platelet count < 50 x 10^9/L (< 50,000/mcL); AND

I) Patient is scheduled to undergo a procedure within 10 to 13 days after starting Doptelet therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Doptelet is not recommended in the following situations:

110. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

85. Doptelet® tablets [prescribing information]. Durham, NC: AkaRx/Dova; July 2021.
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PRIOR AUTHORIZATION POLICY

POLICY: Thrombocytopenia – Mulpleta Prior Authorization Policy
- Mulpleta® (lusutrombopag tablets – Shionogi/Quotient)

REVIEW DATE: 04/12/2023

OVERVIEW

Mulpleta, a thrombopoietin receptor agonist, is indicated for the treatment of **thrombocytopenia** in adults with **chronic liver disease** who are scheduled to undergo a procedure.[1]

Begin Mulpleta dosing 8 to 14 days before the scheduled procedure. The recommended dose is 3 mg once daily with or without food for 7 days. In the pivotal clinical studies for the approved indication, patients had a platelet count < 50 x 10^9/L.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Mulpleta. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mulpleta is recommended in those who meet the following criteria:

FDA-Approved Indication

15. Thrombocytopenia in a Patient with Chronic Liver Disease. Approve for 7 days if the patient meets the following criteria (A, B, and C):
- **J)** Patient is ≥ 18 years of age; AND
- **K)** Patient has a current platelet count < 50 x 10^9/L (< 50,000/mcL); AND
- **L)** Patient is scheduled to undergo a procedure within 8 to 14 days after starting Mulpleta therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mulpleta is not recommended in the following situations:

111. Chronic Immune Thrombocytopenia. Data are not available regarding use of Mulpleta in patients with persistent and chronic immune thrombocytopenia. Many other agents are FDA-approved for this condition and are recommended in standard guidelines and have established efficacy and safety.[2]

112. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

87. Mulpleta® tablets [prescribing information]. Florham Park, NJ and Philadelphia, PA: Shionogi and Quotient; April 2020.
88. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv*. 2019;3(23):3829-3866.

PRIOR AUTHORIZATION POLICY

POLICY: Thrombocytopenia – Nplate Prior Authorization Policy
- Nplate® (romiplostim subcutaneous injection – Amgen)

REVIEW DATE: 04/12/2023

OVERVIEW

Nplate, a thrombopoietin receptor agonist, is indicated for the treatment of:[1]

- **Hematopoietic syndrome of acute radiation syndrome**, to increase survival in adults and pediatric patients (including term neonates) acutely exposed to myelosuppressive doses of radiation.
- **Immune thrombocytopenia (ITP), in adults** who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
- **Immune thrombocytopenia (ITP), in pediatric patients ≥ 1 year of age** with ITP for at least 6 months who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Nplate should only be utilized in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. Nplate should not be used in an attempt to normalize platelet counts.

Guidelines

Nplate is mentioned in various clinical guidelines.

- **Chemotherapy Induced Thrombocytopenia:** The National Comprehensive Cancer Network (NCCN) guidelines for hematopoietic growth factors (version 2.2023 – March 6, 2023) recommend consideration of Nplate for the management of suspected chemotherapy induced thrombocytopenia (category 2A) in addition to other modalities (e.g., platelet transfusion, chemotherapy dose reduction, or change in treatment regimen).[14]
- **Immune Thrombocytopenia:** The American Society of Hematology has updated guidelines for ITP (2019). For adults with ITP for at least 3 months who are corticosteroid-dependent or unresponsive to a corticosteroid, a thrombopoietin receptor agonist (Nplate or Promacta® [eltrombopag tablets and oral suspension]) or a splenectomy are recommended.[2] In children with newly diagnosed ITP who have non-life-threatening mucosal bleeding, corticosteroids are recommended. For children who have non-life-threatening mucosal bleeding and do not respond to first-line treatment, thrombopoietin receptor agonists are recommended.
- **Myelodysplastic Syndrome (MDS):** NCCN recommendations regarding MDS (version 1.2023 – September 12, 2022) state to consider treatment with a thrombopoietin receptor agonist in patients with lower-risk MDS who have severe or life-threatening thrombocytopenia.[3] Data are available that describe the use of Nplate in patients with MDS.[4-13] The data with Nplate are discussed noting an increased rate of platelet response and decreased overall bleeding events among patients with low to intermediate risk MDS.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Nplate. All approvals are provided for the duration noted below. Regarding the approval duration of one dose, the approval is for 30 days, which is an adequate duration for the patient to receive one dose. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nplate as well as the monitoring required for adverse events and efficacy, approval for some indications requires Nplate to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Nplate is recommended in those who meet one of the following criteria:

FDA-Approved Indications

7. **Hematopoietic Syndrome of Acute Radiation Syndrome.** Approve for one dose if the patient has been acutely exposed to myelosuppressive doses of radiation.

8. **Immune Thrombocytopenia.** Approve if the patient meets one of the following criteria (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets all of the following criteria (i, ii, and iii):
     - **i.** Patient meets one of the following (a or b):
       - **a)** Patient has a platelet count < 30 x 10^9/L (< 30,000/mcL); OR
       - **b)** Patient meets both of the following [(1) and (2)]:
         - Patient has a platelet count < 50 x 10^9/L (< 50,000/mcL); AND
         - According to the prescriber the patient is at an increased risk of bleeding; AND
     - **ii.** Patient meets one of the following (a or b):
       - **a)** Patient has tried at least one other therapy; OR
         Note: Examples of therapies are systemic corticosteroids, intravenous immunoglobulin, anti-D immunoglobulin, Promacta (eltrombopag tablets and oral suspension), Tavalisse (fostamatinib tablets), Doptelet (avatrombopag tablets), or ritixumab.
       - **b)** Patient has undergone splenectomy; AND
     - **iii.** Medication is prescribed by or in consultation with a hematologist; OR
   - **B)** Patient is Currently Receiving Nplate. Approve for 1 year if the patient meets both of the following criteria (i and ii):
     - **iii.** According to the prescriber the patient demonstrates a beneficial clinical response; AND
       Note: A beneficial response can include increased platelet counts, maintenance of platelet counts, and/or a decreased frequency of bleeding episodes.
     - **iv.** Patient remains at risk for bleeding complications.

Other Uses with Supportive Evidence

3. **Thrombocytopenia, Chemotherapy-Induced.** Approve if the patient meets one of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets all of the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has a platelet count < 100 x 10^9/L (< 100,000/mcL); AND
     - **iii.** Patient meets one of the following (a or b):

a) Patient has thrombocytopenia at least 3 weeks after the most recent dose of chemotherapy; OR

b) Patient has experienced a delay in chemotherapy administration related to thrombocytopenia; AND

iv. Medication is prescribed by or in consultation with a hematologist or an oncologist; OR

B) Patient is Currently Receiving Nplate. Approve for 6 months if the patient meets the following criteria (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient continues to receive treatment with chemotherapy; AND

iii. Patient demonstrates a beneficial clinical response according to the prescriber.

Note: A beneficial response can include increased platelet counts, maintenance of platelet counts, and/or decreased frequency of bleeding episodes.

4. Thrombocytopenia in Myelodysplastic Syndrome. Approve if the patient meets one the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets all of the following criteria (i, ii, and iii):

i. Patient has low- to intermediate-risk myelodysplastic syndrome; AND

ii. Patient meets one of the following (a or b):

a) Patient has a platelet count < 30 x 10^9/L (< 30,000/mcL); OR

b) Patient meets both of the following [(1) and (2)]:

(1) Patient has a platelet count < 50 x 10^9/L (< 50,000/mcL); AND

(2) According to the prescriber the patient is at an increased risk for bleeding; AND

iii. Medication is prescribed by or in consultation with a hematologist or an oncologist; OR

B) Patient is Currently Receiving Nplate. Approve for 1 year if the patient meets both of the following criteria (i and ii):

i. According to the prescriber the patient demonstrates a beneficial clinical response; AND

Note: A beneficial response can include increased platelet counts, maintenance of platelet counts, and/or decreased frequency of bleeding episodes.

ii. Patient remains at risk for bleeding complications.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nplate is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

201. Nplate® subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; February 2022.
202. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv*. 2019;3(23):3829-3866.
203. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (Version 1.2023 – September 12, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 12, 2023.
204. Giagounidis A, Mufti GJ, Fenaux P, et al. Results of a randomized, double-blind study of romiplostim versus placebo in patients with low/intermediate-1-risk myelodysplastic syndrome and thrombocytopenia. *Cancer*. 2014;120:1838-1846.
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209. Kantarjian H, Fenaux P, Sekeres MA, et al. Safety and efficacy of romiplostim in patients with lower-risk myelodysplastic syndrome and thrombocytopenia. *J Clin Oncol*. 2010;28(3):437-444.
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211. Kantarjian HM, Fenaux P, Sekeres MA, et al. Long-term follow-up for up to 5 years on the risk of leukaemic progression in thrombocytopenic patients with lower-risk myelodysplastic syndromes treated with romiplostim or placebo in a randomized double-blind trial. *Lancet Haematol*. 2018;5(3):e117-e126.
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213. Prica A, Sholzberg M, Buckstein R. Safety and efficacy of thrombopoietin-receptor agonists in myelodysplastic syndromes: a systematic review and meta-analysis of randomized controlled trials. *Br J Haematol*. 2014;167:626-638.
214. The NCCN Hematopoietic Growth Factors Clinical Practice Guidelines in Oncology (Version 2.2023 – March 6, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 12, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Thrombocytopenia – Promacta Prior Authorization Policy
- Promacta® (eltrombopag tablets and oral suspension – Novartis)

REVIEW DATE: 04/12/2023

OVERVIEW

Promacta, a thrombopoietin receptor agonist, is indicated for the following uses:[1]

- **Aplastic anemia**, severe, in combination with standard immunosuppressive therapy for the first-line treatment of adults and pediatric patients ≥ 2 years of age as well as for treatment in patients who have had an insufficient response to immunosuppressive therapy.
- **Chronic hepatitis C, treatment of thrombocytopenia**, to allow the initiation and maintenance of interferon-based therapy.
- **Immune thrombocytopenia (ITP), treatment, in adults and pediatric patients ≥ 1 year of age** with persistent or chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Of note, Promacta should only be used in patients whose degree of thrombocytopenia and clinical condition increase the risk for bleeding.

For patients with refractory severe aplastic anemia, if no hematologic response has occurred after 16 weeks of treatment with Promacta, discontinue therapy. For ITP, Promacta should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of therapy with Promacta at the maximum daily dose of 75 mg. Use Promacta only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy.[1] The safety and efficacy of Promacta have not been established in combination with direct-acting antiviral agents used without interferon for the treatment of chronic hepatitis C infection. For the management of chronic hepatitis C, Promacta should be stopped upon discontinuation of antiviral treatment futility.

Guidelines

Promacta is addressed in several guidelines.

- **Aplastic Anemia:** Guidelines for the diagnosis and management of adults with aplastic anemia are available from the British Society for Standards in Hematology (2016).[2] Immunosuppressive therapy is recommended first-line for non-severe aplastic anemia in patients requiring treatment, severe or very severe aplastic anemia in patients who lack a matched sibling donor, and severe or very severe aplastic anemia in patients between 35 to 50 years of age. Other recommended immunosuppressives have been studied (e.g., mycophenolate mofetil, sirolimus, corticosteroids) but expertise should be provided prior to consideration of such agents. Hematopoietic stem cell transplantation (HSCT) is also recommended in certain circumstances. Promacta is an option is some clinical scenarios (e.g., heavily pre-treated patients, those unsuitable for HSCT).
- **Immune Thrombocytopenia (ITP):** In 2019, the American Society of Hematology updated guidelines for ITP.[3] There are several recommendations. For adults with ITP for at least 3 months who are corticosteroid-dependent or unresponsive to corticosteroid, a thrombopoietin receptor agonist (Promacta or Nplate® [romiplostim subcutaneous injection]) or a splenectomy are recommended. In children with newly diagnosed ITP who have non-life-threatening mucosal bleeding, corticosteroids are recommended. For children who have non-life-threatening mucosal bleeding and did not respond to first-line treatment, thrombopoietin receptor agonists are

recommended. Other treatment options in children and adults include intravenous immunoglobulin, anti-D immunoglobulin, and rituximab.

- **Myelodysplastic Syndrome (MDS):** Recommendations from the National Comprehensive Cancer Network for MDS (version 1.2023 – September 12, 2022) state that treatment with a thrombopoietin receptor agonist should be considered in patients with lower-risk MDS who have severe or life-threatening thrombocytopenia.[4] The data with Promacta are discussed noting an increased rate of platelet response and decreased overall bleeding events in patients with low- to intermediate-risk MDS. Other data are also available that describe the use of Promacta in patients with MDS.[5-7]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Promacta. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Promacta as well as the monitoring required for adverse events and long-term efficacy, approval requires Promacta to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Promacta is recommended in those who meet one of the following criteria:

FDA-Approved Indications

9. Aplastic Anemia. Approve if the patient meets one of the following criteria (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets the following criteria (i, ii, and iii):

i. Patient has low platelet counts at baseline (pretreatment); AND
Note: An example of a low platelet count is < 30 x 10^9/L (< 30,000/mcL).

ii. Patient meets one of the following criteria (a or b):

a) Patient had tried at least one immunosuppressant therapy; OR
Note: Examples of therapies are cyclosporine, Atgam (lymphocyte immune globulin, anti-thymocyte globulin [equine] sterile solution for intravenous use only), mycophenolate mofetil, or sirolimus.

b) Patient will be using Promacta in combination with standard immunosuppressive therapy; AND
Note: Examples of therapies are cyclosporine, Atgam (lymphocyte immune globulin, anti-thymocyte globulin [equine] sterile solution for intravenous use only), mycophenolate mofetil, or sirolimus.

iii. Promacta is prescribed by or in consultation with a hematologist; OR

B) Patient is Currently Receiving Promacta. Approve for 1 year if, according to the prescriber, the patient demonstrates a beneficial clinical response.
Note: Examples include increases in platelet counts, reduction in red blood cell transfusions, hemoglobin increase, and/or absolute neutrophil count increase.

10. Immune Thrombocytopenia. Approve if the patient meets one of the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets all of the following criteria (i, ii, and iii):

i. Patient meets one of the following criteria (a or b):

a) Patient has a platelet count < 30 x 10^9/L (< 30,000/mcL); OR

b) Patient meets both of the following criteria [(1) and (2)]:

- Patient has a platelet count < 50 x 10^9/L (< 50,000/mcL); AND
- According to the prescriber the patient is at an increased risk for bleeding; AND

ii. Patient meets one of the following criteria (a or b):

a) Patient has tried at least one other therapy; OR

Note: Examples of therapies are systemic corticosteroids, intravenous immunoglobulin, anti-D immunoglobulin, Nplate (romiplostim subcutaneous injection), Tavalisse (fostamatinib tablets), Doptelet (avatrombopag tablets), or rituximab.

b) Patient has undergone splenectomy; AND

iii. The medication is prescribed by or in consultation with a hematologist; OR

B) Patient is Currently Receiving Promacta. Approve for 1 year if the patient meets both of the following criteria (i and ii):

i. According to the prescriber, the patient demonstrates a beneficial clinical response; AND

Note: A beneficial response can include increased platelet counts, maintenance of platelet counts, and/or a decreased frequency of bleeding episodes.

ii. Patient remains at risk for bleeding complications.

11. Thrombocytopenia in a Patient with Chronic Hepatitis C. Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) Patient has low platelet counts at baseline (pretreatment); AND

Note: An example of a low platelet count is < 75 x 10^9/L (< 75,000/mcL).

B) Patient will be receiving interferon-based therapy for chronic hepatitis C; AND

Note: Examples of therapies are pegylated interferon (Pegasys [peginterferon alfa-2a injection], PegIntron [peginterferon alfa-2b injection]), or Intron A (interferon alfa-2b).

C) The medication is prescribed by or in consultation with a gastroenterologist, a hepatologist, or a physician who specializes in infectious disease.

Other Uses with Supportive Evidence

4. Thrombocytopenia in a Patient with Myelodysplastic Syndrome. Approve if the patient meets one of the following criteria (A or B):

B) Initial Therapy. Approve for 3 months if the patient meets the following criteria (i, ii, and, iii):

a. Patient has low- to intermediate-risk myelodysplastic syndrome; AND

b. Patient meets one of the following criteria (a or b):

a) Patient has a platelet count < 30 x 10^9/L (< 30,000/mcL); OR

b) Patient meets one of the following criteria [(1) and (2)]:

(1) Patient has a platelet count < 50 x 10^9/L (< 50,000/mcL); AND

(2) According to the prescriber, the patient is at an increased risk for bleeding; AND

c. The medication is prescribed by or in consultation with a hematologist or an oncologist; OR

B) Patient is Currently Receiving Promacta. Approve for 1 year if the patient meets both of the following criteria (i and ii):

iii. According to the prescriber, the patient demonstrates a beneficial clinical response; AND

Note: A beneficial response can include increased platelet counts, maintenance of platelet counts, and/or decreased frequency of bleeding episodes.

iv. Patient remains at risk for bleeding complications.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Promacta is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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PRIOR AUTHORIZATION POLICY

POLICY: Thrombocytopenia – Tavalisse Prior Authorization Policy
- Tavalisse® (fostamatinib disodium hexahydrate tablets – Rigel/Patheon Whitby)

REVIEW DATE: 04/12/2023

OVERVIEW

Tavalisse, a tyrosine kinase inhibitor with demonstrated activity against spleen tyrosine kinase, is indicated for the treatment of thrombocytopenia in adults with **chronic immune thrombocytopenia** (ITP) who have had an insufficient response to a previous treatment.[1]

The safety and efficacy of Tavalisse have not been established in pediatric patients. Use of Tavalisse is not recommended for patients < 18 years of age because adverse events on actively growing bones were observed in nonclinical studies. Discontinue Tavalisse if after 12 weeks of treatment, the platelet count does not increase to a sufficient level to control bleeding.

Guidelines

In 2019, the American Society of Hematology updated guidelines for ITP.[2] Tavalisse is noted as an agent that has been studied in the third-line setting and its role is not specifically addressed. However, there are several other recommendations. For adults with ITP for at least 3 months who are corticosteroid-dependent or unresponsive to corticosteroid, a thrombopoietin receptor agonist (either Promacta® [eltrombopag tablets and oral suspension] or Nplate® [romiplostim subcutaneous injection]) or a splenectomy are recommended. Other treatment options in children and adults include intravenous immunoglobulin, anti-D immunoglobulin, and rituximab.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tavalisse. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tavalisse as well as the monitoring required for adverse events and long-term efficacy, approval requires Tavalisse to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tavalisse is recommended in those who meet the following criteria:

FDA-Approved Indication

16. Chronic Immune Thrombocytopenia. Approve if the patient meets one of the following criteria (A or B):

M) Initial Therapy. Approve for 3 months if the patient meets all of the following criteria (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets one of the following criteria (a or b):
- **a)** Patient has a platelet count < 30 x 10^9/L (< 30,000/mcL): OR
- **b)** Patient meets both of the following criteria [(1) and (2)]:
  - **1.** The patient has a platelet count < 50 x 10^9/L (< 50,000/mcL); AND
  - **2.** According to the prescriber, the patient is at an increased risk of bleeding; AND

iii. Patient meets one of the following criteria (a or b):
- (1) Patient has tried at least one other therapy; OR
  Note: Examples of therapies are systemic corticosteroids, intravenous immunoglobulin, anti-D immunoglobulin, Promacta (eltrombopag tablets and oral suspension), Nplate (romiplostim subcutaneous injection), Doptelet (avatrombopag tablets), or rituximab.
- (2) Patient has undergone splenectomy; AND

iv. The medication is prescribed by or in consultation with a hematologist; OR

B) Patient is Currently Receiving Tavalisse. Approve for 1 year if the patient meets both of the following criteria (i and ii):

iii. According to the prescriber, the patient demonstrates a beneficial clinical response; AND
Note: A beneficial response can include increased platelet counts, maintenance of platelet counts, and/or a decreased frequency of bleeding episodes; AND

iv. Patient remains at risk for bleeding complications.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tavalisse is not recommended in the following situations:

5. **B-Cell Lymphomas.** Tavalisse has been investigated in patients with various B-cell lymphomas (e.g., non-Hodgkin's lymphoma, diffuse large B-cell lymphoma [DLBCL]).[3,4] Many other therapies are available for this use.

6. **Rheumatoid Arthritis.** Although Tavalisse has been studied in patients with rheumatoid arthritis, other therapies are more well-established and are recommended in guidelines.[5-9]

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Tolvaptan Products – Jynarque Prior Authorization Policy
- Jynarque® (tolvaptan tablets – Otsuka)

REVIEW DATE: 06/28/2023

OVERVIEW

Jynarque, a selective vasopressin V_2-receptor antagonist, is indicated to slow kidney function decline in adults at risk of rapidly-progressing **autosomal dominant polycystic kidney disease** (ADPKD).[1]

Disease Overview

ADPKD is a heterogeneous, inherited kidney disorder associated with the development of kidney cysts, which result in kidney pain, hypertension, renal failure, and other clinical sequelae.[2-5] The condition is a common cause of end-stage renal disease; however, other organs are also impacted (e.g., hepatic and vascular systems). Progressive kidney enlargement occurs; however, manifestations generally do not occur until later in life (fourth decade) due to compensatory renal mechanisms. If a parent has the condition, a child has a 50% chance of inheritance. Approximately 600,000 people in the US have this condition.

Guidelines

The European Renal Association Working Groups on Inherited Kidney Disorders, the European Rare Kidney Disease Reference Network, and the Polycystic Kidney Disease International published a consensus statement regarding use of tolvaptan in ADPKD (2022).[7] A confirmed annual estimated glomerular filtration rate decline ≥ 3.0 mL/min/1.73 m^2 over a period of ≥ 4 years defines rapid progression. Also, a Mayo Classification of 1D or 1E indicates rapid disease progression. Patients with Mayo Classification of 1C should be further evaluated for additional evidence of rapid disease progression. Total kidney volume changes should not be used as a marker of progression in individual patients. Finally, Jynarque should be discontinued when the patient approaches kidney failure (i.e., the need for renal replacement therapy).

The National Kidney Foundation and the Polycystic Kidney Disease Foundation list tolvaptan as an FDA-approved treatment option for patients with ADPKD.[5,8]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Jynarque. All approvals are provided for the duration noted below. Due to the specialized skills required for evaluation and diagnosis of patients treated with Jynarque as well as the monitoring required for adverse events and long-term efficacy, approval requires Jynarque to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Jynarque is recommended in those who meet the following:

FDA-Approved Indication

17. **Autosomal Dominant Polycystic Kidney Disease.** Approve for 1 year if the patient meets the following (A, B, C, and D):
    N) Patient is ≥ 18 years of age; AND
    O) According to the prescriber, the patient has rapidly-progressing autosomal dominant polycystic kidney disease; AND
    Note: Examples of rapidly declining renal function include estimated glomerular filtration rate decline of ≥ 3.0 mL/min/1.73 m^2, and Mayo Classification of 1D or 1E.
    P) Patient does not have Stage 5 chronic kidney disease; AND
    Note: Stage 5 chronic kidney disease is defined as glomerular filtration rate < 15 mL/min/1.73 m^2 or receiving dialysis.
    Q) The medication is prescribed by or in consultation with a nephrologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Jynarque is not recommended in the following situations:

8. **Patient is Currently Receiving Samsca (tolvaptan tablets).** Samsca is a tolvaptan product that is indicated for the treatment of clinically-significant hypervolemic and euvolemic hyponatremia, including patients with heart failure and syndrome of inappropriate antidiuretic hormone (SIADH).[6] Concomitant use is not recommended.

9. **Hyponatremia.** Samsca is another tolvaptan product indicated for the treatment of clinically-significant hypervolemic and euvolemic hyponatremia (serum sodium < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction and fluid restriction), including patients with heart failure and SIADH. Samsca should be used for this condition.

10. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

116. Jynarque® tablets [prescribing information]. Rockville, MD: Otsuka; October 2020.
117. Chapman AB, Devuyst O, Eckardt KU, et al. Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2015;88:17-27.
118. Ong ACM, Devuyst O, Knebelmann B, et al, on behalf of the ERA-EDTA Working Group for Inherited Kidney Diseases. Autosomal dominant polycystic kidney disease: the changing face of clinical management. *Lancet*. 2015;385:1993-2002.
119. Harris PC, Torres VE. Polycystic Kidney Disease, Autosomal Dominant. In Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Last Updated: July 19, 2018. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1246/ Accessed on June 9, 2022.
120. National Kidney Foundation. Polycystic kidney disease. Available at: https://www.kidney.org/atoz/content/polycystic. Accessed on June 9, 2022.
121. Samsca® tablets [prescribing information]. Rockville, MD: Otsuka; June 2018.
122. Muller RU, Messchendorp AL, Birn H, et al. An update on the use of tolvaptan for autosomal dominant polycystic kidney disease: Consensus statement on behalf of the ERA Working Group on Inherited Kidney Disorders, the European Rare Kidney Disease Reference Network and Polycystic Kidney Disease International. *Nephrol Dial Transplant*. 2022;37:825-839.
123. Polycystic Kidney Disease Foundation. Tolvaptan. Available at: https://pkdcure.org/tolvaptan/. Accessed on June 8, 2022.

PRIOR AUTHORIZATION POLICY

POLICY: Tolvaptan Products – Tolvaptan (Samsca) Prior Authorization Policy
- Samsca® (tolvaptan tablets – Otsuka, generic)

REVIEW DATE: 06/28/2023

OVERVIEW

Tolvaptan (Samsca, generic), a selective vasopressin V_2-receptor antagonist, is indicated for the treatment of **clinically significant hypervolemic and euvolemic hyponatremia** (serum sodium < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure and syndrome of inappropriate antidiuretic hormone (SIADH). Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with Samsca. It has not been established that raising serum sodium with Samsca provides a symptomatic benefit to patients.

Clinical Data

Two trials (Study of Ascending Levels of Tolvaptan in Hyponatremia 1 and 2 [SALT-1 and SALT-2; n = 424]) demonstrated that Samsca increased serum sodium effectively in patients with euvolemic or hypervolemic hyponatremia that was due to many underlying causes (e.g., heart failure, liver cirrhosis, SIADH).[1,2] Patients ≥ 18 years of age received therapy for 30 days with Samsca or placebo and were followed for an additional 7 days after study withdrawal. Patients in the trial had a serum sodium < 135 mEq/L at study entry (baseline 129 mEq/L). In both trials, Samsca therapy led to a greater increase in serum sodium compared with baseline for the measured endpoints at Day 4 and Day 30. The effects of sustained serum sodium were demonstrated for up to 1 year in an open-label study.[1]

SALTWATER (the Safety and sodium Assessment of Long-term Tolvaptan With hyponatremia: A year-long, open-label Trial to gain Experience under Real-world conditions [SALTWATER]) was an open-label extension study of the SALT-1 and SALT-2 trials.[1,3] Patients were eligible if they had completed either SALT-1 or SALT-2 and had a need and desire to continue therapy. There were 111 patients enrolled in the study with a mean baseline serum sodium concentration of 130.8 ± 4.4 mmol/L. Patients received Samsca for a mean of 701 days (1.92 years). Serum sodium concentrations increased to a mean of > 135 mmol/L by Day 14 and remained above this level at all observation time points going forward. Upon discontinuation of tolvaptan, the serum sodium concentration declined by ≥ 3 mmol/L in 68% of patients and an equal amount had serum sodium concentrations fall to < 135 mmol/L. One patient discontinued tolvaptan due to hypernatremia.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of tolvaptan. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of tolvaptan is recommended in those who meet the following criteria:

FDA-Approved Indication

12. Hyponatremia. Approve for the duration noted if patient meets ONE of the following (A or B):
- **A)** Initial Therapy. Approve for 30 days if the patient meets the following (i and ii):
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** Patient meets ONE of the following criteria (a, b, or c):
    - **a)** Patient has a serum sodium < 125 mEq/L at baseline; OR
    - **b)** Patient meets the following criteria [(1) and (2)]:
      - **(1)** Patient has less marked hyponatremia, defined as serum sodium < 135 mEq/L at baseline; AND
      - **(2)** Patient has symptomatic hyponatremia; OR
        Note: Symptoms of hyponatremia include nausea, vomiting, headache, lethargy, confusion.
    - **c)** Patient has already been started on tolvaptan and has received < 30 days of therapy.
      Note: For a patient who has been started on tolvaptan and has received < 30 days of therapy, approve for a sufficient duration to complete 30 total days of therapy.
- **B)** Patient is Currently Receiving Tolvaptan. Approve for 3 months if the patient meets the following (i and ii):
  - **i.** Patient has been established on therapy for at least 30 days; AND
    Note: A patient who has received < 30 days of therapy or is restarting therapy is reviewed under criterion A (Initial Therapy).
  - **ii.** Patient meets at least one of the following (a or b):
    - **a)** According to the prescriber, the serum sodium level has increased from baseline (prior to initiating the requested drug); OR
    - **b)** According to the prescriber, patient experienced improvement in at least one symptom, such as nausea, vomiting, headache, lethargy, or confusion.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of tolvaptan is not recommended in the following situations:

11. Autosomal Dominant Polycystic Kidney Disease (ADPKD). Jynarque® (tolvaptan tablets) is another tolvaptan product that is indicated to slow kidney function decline in adults at risk of rapidly-progressing ADPKD. The recommended dosing differs.[4] The Samsca prescribing information states that tolvaptan should not be prescribed or used to treat ADPKD outside of the FDA-approved Risk Evaluation and Mitigation Strategies for ADPKD.[1]

12. Patient is Currently Receiving Jynarque. Jynarque is another tolvaptan product that is indicated to slow kidney function decline in adults at risk of rapidly-progressing ADPKD. Concomitant use is not recommended.

13. Patients Requiring Intervention to Raise Serum Sodium Urgently to Prevent or to Treat Serious Neurological Symptoms. Samsca has not been studied in a setting of urgent need to raise serum sodium acutely.[1]

14. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

222. Samsca® tablets [prescribing information]. Rockville, MD: Otsuka; April 2021.
223. Schrier RW, Gross P, Gheorghiade M, et al, for the SALT Investigators. Tolvaptan, a selective oral vasopressin V_2-receptor antagonist, for hyponatremia. *N Engl J Med*. 2006;355:2099-2112.
224. Berl T, Quittnat-Pelletier F, Verbalis JG, et al, for the SALTWATER Investigators. Oral tolvaptan is safe and effective in chronic hyponatremia. *J Am Soc Nephrol*. 2010;21:705-712.
225. Jynarque® tablets [prescribing information]. Rockville, MD: Otsuka; October 2020.

PRIOR AUTHORIZATION POLICY

POLICY: Topical Acne – Winlevi Prior Authorization Policy
- Winlevi® (clascoterone 1% cream – Sun)

REVIEW DATE: 12/20/2023

OVERVIEW

Winlevi, an androgen receptor inhibitor, is indicated for the topical treatment of **acne vulgaris** in patients ≥ 12 years of age.[1]

Safety

Winlevi is the only topical acne product with a Warning about hypothalamic-pituitary-adrenal (HPA) axis suppression.[1] This may result when Winlevi is used over large surface areas or if use is prolonged. In addition, pediatric patients may be more susceptible. This adverse event was not observed in the pivotal studies or in the long-term open-label extension study. However, it was observed in a small group of patients on Day 14 in a pharmacokinetic study. Normal HPA axis function was observed at follow-up at 4 weeks after end of treatment.

Guidelines

The most recent guidelines for management of acne from the American Academy of Dermatology was published in 2016, before the approval of Winlevi.[2] Topical therapies, either as monotherapy or in combination with other topical agents or oral agents, are recommended for initial control and maintenance therapy of acne. Topical retinoids (tretinoin, adapalene, tazarotene) are the cornerstone of acne management due to their comedolytic and anti-inflammatory properties. Other topical therapies mentioned in the guidelines for management and treatment of acne include antibiotics (e.g., clindamycin, erythromycin), azelaic acid, dapsone, and salicylic acid.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Winlevi. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Winlevi is recommended in those who meet the following criteria:

FDA-Approved Indication

1. Acne Vulgaris. Approve for 1 year if the patient meets the following (A, B, and C):
- **13.** Patient is ≥ 12 years of age; AND
- **14.** Patient has tried at least one prescription topical retinoid.

QQQ) Note: Examples of a prescription topical retinoid are adapalene (Differin, generic), Aklief (trifarotene 0.005% cream), tazarotene 0.1% cream (Tazorac, generic), taxarotene 0.1% gel (Tazorac, generic), and tretinoin; AND
- **15.** Patient has tried at least three other prescription topical therapies.

Note: Examples of other prescription topical therapies for acne include: dapsone gel (Aczone, generic), Azelex (azelaic acid 20% cream), topical clindamycin, topical erythromycin, and topical minocycline (Amzeeq [minocycline 4% foam]).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Winlevi is not recommended in the following situations:

15. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Winlevi® cream [prescribing information]. Cranbury, NJ: Sun; July 2022.
2. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol.* 2016;74:945-73.

PRIOR AUTHORIZATION POLICY

POLICY: Topical Acyclovir Products Prior Authorization Policy
- Zovirax® (acyclovir 5% cream –Bausch Health, generic)
- Zovirax® (acyclovir 5% ointment – Bausch Health, generic)

REVIEW DATE: 07/26/2023

OVERVIEW

Acyclovir 5% cream (Zovirax, generic) is indicated for the treatment of **recurrent herpes labialis (cold sores)** in immunocompetent patients ≥ 12 years of age.[1]

Acyclovir 5% ointment (Zovirax, generics) is indicated for the following uses:[2]
- **Genital herpes**, initial treatment.
- **Limited non-life-threatening mucocutaneous herpes simplex virus infections**, in immunocompromised patients.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of topical acyclovir products. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of acyclovir 5% cream (Zovirax 5% cream, generic) is recommended in those who meet the following criteria:

FDA-Approved Indication

3. Herpes Labialis (Cold Sores). Approve for 1 year if the patient meets the following (A and B):
- **a)** Patient is ≥ 12 years of age; AND
- **b)** Patient is immunocompetent.

II. Coverage of acyclovir 5% ointment (Zovirax 5% ointment, generic) is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Genital Herpes. Approve for 1 year if the patient meets one of the following (A or B):
- **A)** Generic acyclovir 5% ointment is requested; OR
- **B)** Patient meets the following (i and ii):
  - **i.** Patient has tried generic acyclovir 5% ointment; AND
  - **ii.** Patient cannot use the generic product due to a formulation difference in the inactive ingredient(s) [e.g., difference in buffers, emollients, emulsifiers, preservatives, surfactants]

between the brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

2. **Limited Non-Life-Threatening Mucocutaneous Herpes Simplex Virus Infections.** Approve for 1 year if the patient meets one of the following (A and B):
   - **A)** Patient is immunocompromised; AND
   - **B)** Patient meets one of the following (i or ii):
     - **i.** Generic acyclovir 5% ointment is requested; OR
     - **ii.** Patient meets the following criteria (a and b):
       - **a)** Patient has tried generic acyclovir 5% ointment; AND
       - **b)** Patient cannot use the generic product due to a formulation difference in the inactive ingredient(s) [e.g., difference in buffers, emollients, emulsifiers, preservatives, surfactants] between the brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of topical acyclovir products are not recommended in the following situation:

1. **Shingles (Herpes Zoster).** Shingles is a viral infection caused by the varicella zoster virus, the same virus that causes chickenpox.[3] The Centers for Disease Control and Prevention cite the use of oral antivirals (acyclovir capsules/tablets/suspension, famciclovir tablets, and valacyclovir caplets) for the treatment of shingles. Oral antivirals speed healing and reduce the risk of complications. Topical antivirals are not noted as treatment options for shingles.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Zovirax® cream [prescribing information]. Bridgewater, NJ: Bausch Health; February 2021.
2. Zovirax® ointment [prescribing information]. Bridgewater, NJ: Bausch Health; October 2020.
3. Centers for Disease Control and Prevention – Shingles. Available at: https://www.cdc.gov/shingles/about/treatment.html. Updated May 2023. Accessed on July 18, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Topical Alpha-Adrenergic Agonists for Rosacea – Brimonidine Prior Authorization Policy
- Mirvaso® (brimonidine gel, 0.33% – Galderma, generic)

REVIEW DATE: 01/25/2023; selected revision 03/01/2023

OVERVIEW

Brimonidine 0.33% gel, an alpha$_2$-adrenergic agonist, is indicated for the topical treatment of persistent (non transient) **facial erythema of rosacea** in patients ≥ 18 years of age.[1]

Brimonidine 0.33% gel has been shown to decrease the erythema associated with rosacea; brimonidine 0.33% gel has not been shown to exert any beneficial effects on inflammatory lesions.[1-3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Mirvaso/brimonidine 0.33% gel. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mirvaso/brimonidine 0.33% gel is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Facial Erythema.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has facial erythema due to rosacea.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mirvaso/brimonidine 0.33% gel is not recommended in the following situations:

16. **Erythema Caused by Conditions Other Than Rosacea**.

17. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Mirvaso® topical gel [prescribing information]. Fort Worth, TX: Galderma; November 2017.
2. Del Rosso JQ, Thiboutot D, Gallo R, et al. Consensus recommendations from the American Acne & Rosacea Society on the management of rosacea, part 2: a status report on topical agents. *Cutis.* 2013;92(6):277-284.
3. Del Rosso JQ, Thiboutot D, Gallo R, et al. Consensus recommendations from the American Acne & Rosacea Society on the management of rosacea, part 5: a guide on the management of rosacea. *Cutis.* 2014;93(3):134-138.

PRIOR AUTHORIZATION POLICY

POLICY: Topical Alpha-Adrenergic Agonists for Rosacea – Rhofade Prior Authorization Policy
- Rhofade® (oxymetazoline 1% hydrochloride cream – EPI Health)

REVIEW DATE: 06/28/2023

OVERVIEW

Rhofade, an alpha$_{1A}$-adrenergic agonist, is indicated for the topical treatment of persistent **facial erythema associated with rosacea** in adults.[1]

Rhofade has been shown to decrease the erythema associated with rosacea and has not been shown to exert any beneficial effects on inflammatory lesions.[1-3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Rhofade. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rhofade is recommended in those who meet the following criteria:

FDA-Approved Indication

2. Facial Erythema. Approve for 1 year if the patient meets both of the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has facial erythema associated with rosacea.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rhofade is not recommended in the following situations:

18. Erythema Caused by Conditions Other Than Rosacea.

19. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

226. Rhofade® cream for topical use [prescribing information]. Charleston, SC: EPI Health; November 2019.
227. Del Rosso JQ, Thiboutot D, Gallo R, et al. Consensus recommendations from the American Acne & Rosacea Society on the management of rosacea, part 2: a status report on topical agents. *Cutis.* 2013;92(6):277-284.
228. Del Rosso JQ, Thiboutot D, Gallo R, et al. Consensus recommendations from the American Acne & Rosacea Society on the management of rosacea, part 5: a guide on the management of rosacea. *Cutis.* 2014;93(3):134-138.

PRIOR AUTHORIZATION POLICY

POLICY: Topical Anesthetic – Lidocaine, Tetracaine Products Prior Authorization with Step Therapy Policy
- Pliaglis® (lidocaine 7%/tetracaine 7% topical cream – Taro/Oba, generic)
- Synera® (lidocaine 70 mg/tetracaine 70 mg topical patches – Galen [obsolete 2022])

REVIEW DATE: 05/24/2023

OVERVIEW

Lidocaine 7%/tetracaine 7% topical cream (Pliaglis, generic) is indicated to provide topical local analgesia for **superficial dermatological procedures** (e.g., dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, laser-assisted tattoo removal) in adults, for use on intact skin.[1]

Synera is indicated to provide local dermal analgesia in patients ≥ 3 years of age on intact skin for the following uses:[2]
- **Superficial dermatological procedures**.
- **Venipuncture or intravenous cannulation**.

Lidocaine cream and combination lidocaine/prilocaine cream are other topical local anesthetics used for various conditions.[3,4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of lidocaine 7%/tetracaine 7% topical cream (Pliaglis, generic) and Synera. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of lidocaine 7%/tetracaine 7% topical cream (Pliaglis, generic) is recommended in those who meet the following criteria:

FDA-Approved Indication

17. Superficial Dermatological Procedures. Approve for 1 week if the patient meets all of the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The procedure is for a non-cosmetic condition; AND
- **C)** The medication will be applied to intact skin; AND
- **D)** Patient has tried both of the following topical anesthetics (i and ii):
  - **i.** One lidocaine cream product; AND
  - **ii.** One lidocaine/prilocaine cream product.

II. Coverage of Synera is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Superficial Dermatological Procedures.** Approve for 1 week if the patient meets all of the following criteria (A, B, C, and D):
   - **A)** Patient is ≥ 3 years of age; AND
   - **B)** The procedure is for a non-cosmetic condition; AND
   - **C)** The medication will be applied to intact skin; AND
   - **D)** Patient has tried both of the following topical anesthetics (i and ii):
     - **i.** One lidocaine cream product; AND
     - **ii.** One lidocaine/prilocaine cream product.

2. **Venipuncture or Intravenous Cannulation.** Approve for 1 week if the patient meets all of the following criteria (A, B, and C):
   - **A)** Patient is ≥ 3 years of age; AND
   - **B)** The medication will be applied to intact skin; AND
   - **C)** Patient has tried both of the following topical anesthetics (i and ii):
     - **i.** One lidocaine cream product; AND
     - **ii.** One lidocaine/prilocaine cream product.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of lidocaine 7%/tetracaine 7% topical cream (Pliaglis, generic) and Synera is not recommended in the following situations:

97. Cosmetic Conditions. Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical pharmacy benefit.
Note: Examples of cosmetic conditions include dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal.

98. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

243. Pliaglis® cream [prescribing information]. Hawthorne, NY: Taro; January 2021.
244. Synera® patches [prescribing information]. Souderton, PA: Galen; December 2020.
245. Lidocaine cream [prescribing information]. Livonia, MI: Rugby; March 2020.
246. Lidocaine and prilocaine cream [prescribing information]. Bridgewater, NJ: Amneal; April 2019.

PRIOR AUTHORIZATION POLICY

POLICY: Topical Diclofenac Sodium 3% Gel Prior Authorization Policy
- diclofenac sodium 3% gel (generic only)

REVIEW DATE: 08/16/2023

OVERVIEW

Diclofenac sodium 3% gel, a nonsteroidal anti-inflammatory drug, is indicated for the topical treatment of **actinic keratoses**.[1] It is also noted in the labeling that sun avoidance is indicated during therapy.

Guidelines

The National Comprehensive Cancer Network (NCCN) Squamous Cell Skin Cancer guidelines (version 1.2023 – March 10, 2023) cite topical diclofenac (formulation is not specified) as a treatment option for the treatment of actinic keratoses.[2] The guidelines also note diclofenac as a (potential) treatment option for the treatment of actinic keratosis on the lips (actinic cheilitis); other treatment options are: surgical vermillionectomy, lip shave, electrodessication, laser vermilion ablation, laser resurfacing, 5-fluorouracil, laser + 5-fluorouracil, trichloroacetic acid chemical peel, photodynamic therapy, and photodynamic therapy plus imiquimod.

Other Uses

Disseminated Superficial Actinic Porokeratosis (DSAP)

Diclofenac gel is noted as a treatment that may be effective for DSAP.[3] Pharmacologic treatment options for DSAP include topical 5-fluorouracil, topical vitamin D_3 analogs, topical imiquimod, topical tacrolimus, oral retinoids (e.g., isotretinoin, acitretin) and topical retinoids (tretinoin, tazarotene), and diclofenac. Diclofenac was studied in an open-label study where patients (n = 17) received 12 weeks of therapy with diclofenac sodium 3% gel and at the end of 12 weeks, treatment could be extended for an additional 12 weeks.[4] At Week 12, the target area lesions (treated lesions) had a mean reduction of 4% vs. a 12% mean increase in the total body lesions (global). Ten patients received 24 weeks of treatment and there was a mean increase of 10% in lesions in the target area vs. a 19% increase in global lesions.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of diclofenac sodium 3% gel. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of diclofenac sodium 3% gel is recommended in those who meet one of the following criteria:

FDA-Approved Indication

16. Actinic Keratoses. Approve for 6 months.

Other Uses with Supportive Evidence

17. **Actinic Cheilitis (Actinic Keratoses of the Lip[s]).** Approve for 6 months.

3. **Disseminated Superficial Actinic Porokeratosis.** Approve for 6 months if the patient has tried at least two other therapies used for the management of disseminated superficial actinic porokeratosis. Note: Examples of therapies for management of disseminated superficial actinic porokeratosis include topical 5-fluorouracil (5-FU), imiquimod, topical corticosteroids, topical vitamin D_3 analogs, topical or oral retinoids, cryotherapy, photodynamic therapy, and laser.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of diclofenac sodium 3% gel is not recommended in the following situations:

20. **Osteoarthritis (OA).** The benefit of topical diclofenac gel 3% in osteoarthritis is uncertain. There has been one small, randomized, placebo-controlled study assessing the efficacy of a topical diclofenac 3%/sodium hyaluronate 2.5% gel (Canadian formulation) applied as 2 grams four times daily to one joint for 2 weeks in patients (n = 119) with uncontrolled OA pain despite chronic (≥ 1 month) oral nonsteroidal anti-inflammatory drug (NSAID) use.[5] The addition of topical diclofenac 3%/sodium hyaluronate to oral NSAID therapy resulted in only marginally greater analgesic effect than NSAID alone. Other topical agents are indicated for this use.

21. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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232. Marks S, Varma R, Cantrell W, et al. Diclofenac sodium 3% gel as a potential treatment for disseminated superficial actinic porokeratosis. *J Eur Acad Dermatol Venereol.* 2009;23(1):42-45.
233. Roth SH. A controlled clinical investigation of 3% diclofenac/2.5% sodium hyaluronate topical gel in the treatment of uncontrolled pain in chronic oral NSAID users with osteoarthritis. *Int J Tissue React.* 1995;17(4):129-132.

PRIOR AUTHORIZATION POLICY

POLICY: Topical Retinoids – Aklief Prior Authorization Policy
- Aklief® (trifarotene cream – Galderma)

REVIEW DATE: 12/20/2023

OVERVIEW
Aklief, a topical retinoid, is indicated for the topical treatment of **acne vulgaris** in patients ≥ 9 years of age.[1]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Aklief. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Aklief is recommended in those who meet the following criteria:

FDA-Approved Indication

18. Acne Vulgaris. Approve for 1 year if the patient is ≥ 9 years of age.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Aklief is not recommended in the following situations:

22. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

14. Aklief® cream [prescribing information]. Fort Worth, TX: Galderma; January 2022.
15. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol.* 2016;74:945-73.

PRIOR AUTHORIZATION POLICY

POLICY: Topical Retinoids – Panretin Prior Authorization Policy
- Panretin® (alitretinoin topical gel – Eisai)

REVIEW DATE: 08/02/2023

OVERVIEW

Panretin, a topical retinoid, is indicated for the topical treatment of cutaneous lesions in patients with Acquired Immunodeficiency Syndrome (AIDS)-related **Kaposi sarcoma**.[1] It is not indicated when systemic anti-Kaposi sarcoma therapy is required (e.g., more than 10 new Kaposi sarcoma lesions in the prior month, symptomatic lymphedema, symptomatic pulmonary Kaposi sarcoma, or symptomatic visceral involvement). Per the prescribing information, there is no experience to date using Panretin gel with systemic anti-Kaposi sarcoma treatment.

RRR)

SSS) Guidelines

Use of Panretin is addressed in the National Comprehensive Cancer Network guidelines for Kaposi sarcoma (version 1.2023 – December 20, 2022).[2] Topical agents are among the first-line therapy recommendations for symptomatic and/or cosmetically unacceptable cutaneous disease; this applies both for patients with human immunodeficiency virus (HIV) and patients without HIV. Panretin is listed as an option for topical treatment (category 2A).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Panretin. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Panretin, approval requires Panretin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Prior authorization and prescription benefit coverage are not recommended for cosmetic uses.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Panretin is recommended in those who meet the following criteria:

FDA-Approved Indication

4. Kaposi Sarcoma. Approve for 1 year if the patient meets both of the following (A and B):
- **A)** Patient is not receiving systemic therapy for Kaposi sarcoma; AND
- **B)** The medication is prescribed by or in consultation with a dermatologist, oncologist, or infectious disease specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Panretin is not recommended in the following situations:

2. **Cosmetic Uses.** Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical pharmacy benefit.
   Note (this is not an all-inclusive list): Examples of cosmetic conditions include actinic purpura, age spots (also called liver spots, solar lentigines, sun spots), melasma/cholasma, milia, mottled hyperpigmentation, mottled hypopigmentation, photo-aged or photo-damaged skin, pokiloderma (of Civatte), premature aging, scarring, sebaceous hyperplasia, seborrheic keratosis, skin laxity, skin roughness, solar elastosis, solar purpura, stretch marks, and wrinkles.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

234. Panretin® topical gel [prescribing information]. Woodcliff Lake, NJ: Eisai; June 2018.
235. The NCCN Kaposi Sarcoma Clinical Practice Guidelines in Oncology (version 1.2023 – December 20, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 25, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Topical Retinoids – Tazarotene Products Prior Authorization Policy
- Arazlo™ (tazarotene 0.045% lotion – Bausch Health)
- Fabior® (tazarotene 0.1% foam – Mayne Pharma)
- Tazorac® (tazarotene 0.05% cream, 0.05% gel, 0.1% cream, and 0.1% gel – Allergan, generic to 0.1% cream only)

REVIEW DATE: 08/02/2023

OVERVIEW

Tazorac gel is indicated for the following uses:[1]
- **Plaque psoriasis**, in patients with up to 20% body surface area involvement (0.05% and 0.1% strengths).
- **Facial acne vulgaris,** in patients with mild to moderate severity (0.1% strength only).

Tazorac cream is indicated for the following uses:[2]
- **Plaque psoriasis** (0.05% and 0.1% strengths).
- **Acne vulgaris** (0.1% strength only).

Both Arazlo lotion and Fabior foam are indicated for the topical treatment of **acne vulgaris**.[3,4]

In addition to acne vulgaris and plaque psoriasis, topical tazarotene products have been used to treat other medical skin conditions, such as basal cell carcinoma and congenital ichthyoses.[5-13] Topical tazarotene products have also been used to treat cosmetic skin conditions such as wrinkles, premature aging, and treatment of photo-aged or photo-damaged skin.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of topical tazarotene products. All approvals are provided for the duration noted below.

Prior authorization and prescription benefit coverage are not recommended for cosmetic uses.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of topical tazarotene products is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Acne Vulgaris.** Approve for 1 year.

2. **Plaque Psoriasis.** Approve for 1 year.

Other Uses with Supportive Evidence

3. **Treatment of Other Non-Cosmetic Conditions.** Approve for 1 year.
   Note: Examples of other non-cosmetic conditions include: acne keloidalis nuchae, basal cell carcinoma, comedonal acne, cystic acne, cutaneous T-cell lymphoma, ichthyosis (e.g., congenital lamellar, vulgaris, X-linked), keratoderma blennorrhagicum, keratosis (e.g., keratosis follicularis [Darier's disease], keratosis pilaris), mycosis fungoides, nail psoriasis, oral lichen planus, and warts.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of topical tazarotene products is not recommended in the following situations:

1. **Cosmetic Conditions.** Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical pharmacy benefit.
   Note (this is not an all-inclusive list): Examples of cosmetic conditions include actinic purpura, age spots (also called liver spots, solar lentigines, sun spots), melasma/cholasma, milia, mottled hyperpigmentation, mottled hypopigmentation, photo-aged or photo-damaged skin, pokiloderma (of Civatte), premature aging, scarring, sebaceous hyperplasia, seborrheic keratosis, skin laxity, skin roughness, solar elastosis, solar purpura, stretch marks, and wrinkles.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Tazorac® topical gel 0.05%, 0.1% [prescribing information]. Irvine, CA: Allergan; April 2018.
2. Tazorac® cream 0.05%, 0.1% [prescribing information]. Irvine, CA: Allergan; August 2019.
3. Arazlo™ lotion [prescribing information]. Bridgewater, NJ: Bausch Health US; May 2021.
4. Fabior® foam 0.1% [prescribing information]. Greenville, NC: Mayne Pharma; June 2018.
5. DRUGDEX® System. Thomson Reuters (Healthcare) Inc. Available at: http://www.micromedexsolutions.com/home/dispatch. Accessed on July 25, 2023. Search term: tazarotene.
6. Facts and Comparisons® Online. Wolters Kluwer Health, Inc.; 2022. Available at: https://fco.factsandcomparisons.com/lco/action/home. Accessed on July 25, 2023. Search term: tazarotene.
7. Acne Keloidalis Nuchae. Available at: https://www.skinsight.com/skin-conditions/adult/acne-keloidalis-nuchae. Accessed on July 25, 2023.
8. Tanghetti E, Dhawan S, Green L, et al. Clinical evidence for the role of a topical anti-inflammatory agent in comedonal acne: findings from a randomized study of dapsone gel 5% in combination with tazarotene cream 0.1% in patients with acne vulgaris. *Drugs Dermatol*. 2011;10:783-792.
9. Morin CB, Roberge D, Turchin I, et al. Tazarotene 0.1% cream as monotherapy for early-stage cutaneous T-cell lymphoma. *J Cutan Med Surg*. 2016;20:244-248.
10. Del Rosso J. Treatment of keratosis pilaris with topical tazarotene cream. *Pediatrics*. 2005;52:P74.
11. Wennberg E, Richards PQ, Bain PA, et al. Topical treatments for early-stage mycosis fungoides using grading recommendations assessment, development and evaluation (GRADE) criteria: a systematic review. *JAAD Int*. 2021;3:26-41.
12. Petruzzi M, De Benedittis M, Grassi R, et al. Oral lichen planus: a preliminary clinical study on treatment with tazarotene. *Oral Dis*. 2002;8:291-295.
13. Petruzzi M, Lucchese A, Lajolo C, et al. Topical retinoids in oral lichen planus treatment: an overview. *Dermatol*. 2013;226:61-67.
14. Pasch N. Nail psoriasis: a review of treatment options. *Drugs*. 2016;76(6):675-705.
15. Rosen T. A multimodality approach to recalcitrant warts. Available at: https://practicaldermatology.com/articles/2012-aug/a-multimodality-approach-to-recalcitrant-warts. Accessed on July 25, 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Uplizna Prior Authorization Policy
- Uplizna® (inebilizumab-cdon intravenous infusion – Horizon Therapeutics)

REVIEW DATE: 07/12/2023

OVERVIEW

Uplizna, a CD19-directed cytolytic antibody, is indicated for the treatment of **neuromyelitis optica spectrum disorder** (NMOSD) in adults who are anti-aquaporin-4 antibody-positive.[1]

Disease Overview

NMOSD is a rare, relapsing, autoimmune central nervous system inflammatory disorder that can lead to significant morbidity and mortality.[2,3] The predominant symptoms are inflammation of the optic nerve (optic neuritis) and inflammation of the spinal cord (myelitis). Optic neuritis may lead to pain inside the eye and can progress to blindness. Myelitis tends to affect some, and often all, motor, sensory, and autonomic functions (bladder and bowel). Affected patients may experience pain in the spine or limbs, mild to severe paralysis of the lower limbs, and loss of bowel and bladder control. For acute attacks, typical treatment is high-dose intravenous corticosteroids.[2] Plasma exchange may be effective in patients who suffer acute severe attacks and who do not respond to intravenous corticosteroids. For long-term control of the disease (relapse prevention), a variety of immunosuppressive drugs are utilized as first-line therapy; most widely prescribed are corticosteroids, azathioprine, mycophenolate mofetil, and rituximab. Interleukin-6 signaling blocking agents (e.g., Enspryng® [satralizumab-mwge subcutaneous {SC} injection], Actemra [tocilizumab injection for intravenous {IV} or SC use]), Soliris® (eculizumab IV infusion), and IV immunoglobulins are also used for relapse prevention.[3] Note that of the listed agents, only Enspryng and Soliris are FDA-approved for NMOSD.[4,5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Uplizna. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Uplizna as well as the monitoring required for adverse events and long-term efficacy, approval requires Uplizna to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Uplizna is recommended in those who meet the following criteria:

FDA-Approved Indication

18. Neuromyelitis Optica Spectrum Disorder. Approve if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 year if the patient meets the following (i, ii, iii, iv, and v):

- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Diagnosis of neuromyelitis optica spectrum disorder was confirmed by blood serum test for anti-aquaporin-4 antibody positive disease; AND
- **iii.** Patient is currently receiving or has previously tried two of the following systemic therapies (a, b, c, or d):
  - **a)** Azathioprine; OR
  - **b)** Corticosteroid; OR
  - **c)** Mycophenolate mofetil; OR
  - **d)** Rituximab; AND

  Note: An exception to the requirement for a trial of a systemic therapy can be made if the patient has already tried Soliris (eculizumab intravenous infusion) or Enspryng (satralizumab-mwge subcutaneous injection) for neuromyelitis optica spectrum disorder. Patients who have already tried Soliris or Enspryng for neuromyelitis optica spectrum disorder are not required to try another systemic agent.
- **iv.** Patient has a of at least one relapse in the last 12 months or two relapses in the last 2 years; AND
- **v.** The medication is being prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Uplizna. Approve for 1 year if the patient meets the following (i, ii, iii, and iv):

- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Diagnosis of neuromyelitis optica spectrum disorder was confirmed by blood serum test for anti-aquaporin-4 antibody-positive disease; AND
- **iii.** According to the prescriber, patient has had clinical benefit from the use of Uplizna; AND
  Note: Examples of clinical benefit include reduction in relapse rate, reduction in symptoms (e.g., pain, fatigue, motor function), and a slowing progression in symptoms.
- **iv.** The medication is being prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Uplizna is not recommended in the following situations:

99. Concomitant Use With a Rituximab Product, Soliris (eculizumab intravenous infusion), or Enspryng (satralizumab-mwge subcutaneous injection). There is no evidence to support additive efficacy of combining Uplizna with rituximab, Soliris, or Enspryng.

100. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

247. Uplizna® intravenous infusion [prescribing information]. Deerfield, IL: Horizon Therapeutics; July 2021.
248. National Organization for Rare Disorders. Neuromyelitis Optica Spectrum Disorder. Last updated July 27, 2022. Available at: https://rarediseases.org/rare-diseases/neuromyelitis-optica/. Accessed on July 7, 2023.
249. Chan KH, Lee CY. Treatment of neuromyelitis optica spectrum disorders. *Int J Mol Sci*. 2021;22(16):8638.
250. Enspryng® subcutaneous injection [prescribing information]. South San Francisco, CA: Genentech; March 2022.
251. Soliris® intravenous infusion [prescribing information]. Boston, MA: Alexion; November 2020.

PRIOR AUTHORIZATION POLICY

POLICY: Vasculitis – Tavneos Prior Authorization Policy
- Tavneos™ (avacopan capsules – ChemoCentryx)

REVIEW DATE: 11/15/2023

OVERVIEW

Tavneos, a complement 5a receptor antagonist, is indicated as an adjunctive treatment for **severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis** (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with standard therapy including glucocorticoids in adults.[1] Tavneos does not eliminate glucocorticoid use.[1]

Disease Overview

ANCA-associated vasculitis is a group of diseases, which includes GPA (Wegener's granulomatosis), MPA, and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).[2] Patients who have ANCA-associated vasculitis produce antibodies that cause inflammation, which damages small blood vessels. The clinical signs and symptoms vary and affect several organs, such as the kidney, lungs, stomach, and intestine. Many patients are positive for proteinase 3 or myeloperoxidase antibodies.[2] Patients normally undergo two phases of treatment; one designed to induce the remission of symptoms (induction treatment), and a second phase meant to keep patients in remission for as long as possible (maintenance treatment).[2] Response is measured by achieving remission or improvement of signs and symptoms, which can be assessed by improvement in the Birmingham Vasculitis Activity Score. Other indicators of clinical response include improvement in kidney function (i.e. improvement in estimated glomerular filtration rate), or decrease in urinary albumin creatinine ratio.[3]

Clinical Efficacy

The efficacy of Tavneos was evaluated in one Phase III, randomized, double-blind, active-controlled pivotal study that assessed the efficacy of Tavneos in patients with newly diagnosed or relapsing active ANCA-associated vasculitis.[3] Patients were randomized in a 1:1 ratio to receive Tavneos twice daily orally plus prednisone-matching placebo or a tapering oral regimen of prednisone plus Tavneos-matching placebo in a double-dummy design. Patients in both groups also received an immunosuppressive regimen (cyclophosphamide followed by azathioprine or mycophenolate mofetil; or rituximab). Patients included were positive for either proteinase 3 or myeloperoxidase antibodies.[3] Glucocorticoid use was allowed in each treatment group, if needed for certain situations.[3] The primary endpoints were remission at Week 26 and sustained remission at Week 52.[3] This pivotal trial demonstrated that Tavneos was noninferior but not superior to the prednisone taper with respect to remission at Week 26 and was superior to prednisone taper with respect to sustained remission at Week 52.[3]

Guidelines

The American College of Rheumatology/Vasculitis Foundation guidelines (2021) for the management of ANCA-associated vasculitis mention that a clinical trial of Tavneos in patients with GPA and MPA was published.[2] Treatment for ANCA-associated vasculitis is based on the severity of the disease, the disease status, and type. The following are recommendations from the guidelines for active, severe GPA/MPA. For remission induction, the guidelines recommend rituximab with reduced-dose glucocorticoids; cyclophosphamide may be used in certain clinical scenarios (i.e. contraindication or failure with rituximab).[2] If remission is not induced, the guidelines recommend switching to a different remission induction agent. For disease relapse, rituximab is recommended if the patient is not receiving rituximab

for remission maintenance; if the patient is taking rituximab for disease maintenance, the guidelines recommend switching from rituximab to cyclophosphamide.[2]

The European League against Rheumatism (EULAR)/European Renal Association –European Dialysis and Transport Association (2022) also have guidelines for ANCA-associated vasculitis.[4] The guidelines state that Tavneos, in combination with rituximab or cyclosporine may be considered for induction of remission in GPA or MPA as part of a strategy to substantially reduce exposure to glucocorticoids. Tavneos should be stopped after a duration of treatment of 6-12 months as there is no data on the use of Tavneos beyond 1 year, so longer-term use cannot be recommended.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tavneos. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tavneos as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Tavneos to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tavneos is recommended in those who meet the following criteria:

FDA-Approved Indication

18. Anti-Neutrophil Cytoplasmic Autoantibody (ANCA)-Associated Vasculitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

- **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v and vi):
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** Patient has granulomatosis with polyangiitis or microscopic polyangiitis; AND
    Note: Granulomatosis with polyangiitis is also known as Wegener's granulomatosis.
  - **iii.** Patient has active disease; AND
    Note: This includes patients that have newly diagnosed or relapsed disease. This does not include patients already in remission.
  - **iv.** Patient is positive for proteinase 3 antibodies, myeloperoxidase antibodies, or anti-neutrophil cytoplasmic autoantibody (ANCA); AND
  - **v.** Patient is using this medication in combination with at least one immunosuppressant; AND
    Note: Examples of immunosuppressants include rituximab, methotrexate, azathioprine, or mycophenolate mofetil.
  - **vi.** The medication is prescribed by or in consultation with a rheumatologist, nephrologist, or immunologist.
- **B)** Patient is Currently Receiving Tavneos. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** Patient has been established on Tavneos for at least 6 months; AND
  - **iii.** Patient meets at least one of the following (a or b):
    - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Tavneos); OR

Note: Examples of objective measure include improvement in estimated glomerular filtration rate, decrease in urinary albumin creatinine ratio, or improvement in the Birmingham Vasculitis Activity Score [BVAS].

b) Compared with baseline (prior to receiving Tavneos), patient experienced an improvement in at least one symptom, such as joint pain, ulcers, myalgia, persistent cough, skin rash, abdominal pain, or improvement in function or activities of daily living.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tavneos is not recommended in the following situations:

101. Eosinophilic Granulomatosis with Polyangiitis (EGPA). There are no data evaluating Tavneos for EGPA. Patients with this condition were excluded from the pivotal study.
Note: EGPA is also known as Churg-Strauss syndrome.

102. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

252. Tavneos™ capsules [prescribing information]. Cincinnati, OH: ChemoCentryx; October 2021.
253. Chung S, Langford CA, Maz M, et al. 2021 American College of Rheumatology/Vasculitis Foundation guidelines for the management of antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Care and Research. 2021; 73(8):1088-1105.
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255. Hellmich B, Sanchez-Alamo B, Schirmer JH. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. *Ann Rheum Dis.* 2023 Mar 16 [Epub ahead of print].

PRIOR AUTHORIZATION POLICY

POLICY: Vecamyl Prior Authorization Policy
- Vecamyl™ (mecamylamine hydrochloride tablets – Vyera)

REVIEW DATE: 06/14/2023

OVERVIEW

Vecamyl, a nicotinic parasympathetic ganglionic blocker, is indicated for the following uses:[1]
- **Moderately severe to severe essential hypertension**.
- **Uncomplicated malignant hypertension**.

Guidelines

The clinical practice guidelines from the American College of Cardiology (ACC)/American Heart Association (AHA) Task Force (2017) state the prevalence of severe hypertension has been declining, but approximately 12.3% of US adults with hypertension have an average systolic blood pressure ≥ 160 mm Hg or average diastolic blood pressure ≥ 100 mm Hg. Numerous classes of antihypertensive agents are available to treat high blood pressure. Vecamyl is not suggested as a primary or secondary agent in the treatment of hypertension. The ACC/AHA guidelines advise selection among four specific medication classes (thiazide-type diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers) as initial and secondary choices in treatment.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vecamyl. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vecamyl is recommended in those who meet one of the following criteria:

FDA-Approved Indications

19. Essential Hypertension, Moderately Severe to Severe. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient has tried four antihypertensive therapies, each from different pharmacologic classes (e.g., diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers [as single-entity or as combination products]); AND
- **B)** For each of these agents, patient meets one of the following criteria (i or ii):
  - **i.** Patient has had inadequate efficacy; OR
  - **ii.** Patient has experienced adverse event(s) severe enough to warrant discontinuation of this agent, according to the prescriber.

20. Uncomplicated Malignant Hypertension. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient has tried four antihypertensive therapies, each from different pharmacologic classes (e.g., diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers [as single-entity or as combination products]); AND

B) For each of these agents, patient meets one of the following criteria (i or ii):
   - **i.** Patient has had inadequate efficacy; OR
   - **ii.** Patient has experienced adverse event(s) severe enough to warrant discontinuation of this agent, according to the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vecamyl is not recommended in the following situations:

23. Tourette Syndrome. Limited data are available to validate the use of mecamylamine in Tourette Syndrome. A clinical trial has shown mecamylamine to not be an effective treatment for tics or for the total spectrum of symptoms associated with Tourette Syndrome.[4]

24. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

256. Vecamyl™ tablets [prescribing information]. New York, NY: Vyera; January 2021.
257. Whelton P, Carey R, Aronow W, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension.* 2018;71:e13-e115.
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PRIOR AUTHORIZATION POLICY

POLICY: Veregen Prior Authorization Policy
- Veregen® (sinecatechins ointment – Fougera)

REVIEW DATE: 01/18/2023

OVERVIEW

Veregen, a botanical drug product, is indicated for the topical treatment of **external genital and perianal warts** (*Condylomata acuminata*) in immunocompetent patients ≥ 18 years of age.[1]

Guidelines

The Centers for Disease Control and Prevention (CDC) Sexually Transmitted Diseases Treatment Guidelines (2021) detail the patient-applied and provider-applied treatment options for the management of genital warts.[2] The CDC guidelines note that treatment should be guided by wart size, number of lesions, location of the wart(s), the preference of the patient, cost of treatment, convenience, adverse effects, and the experience of the health care provider with the various provider-applied options. There is no definitive evidence available which has demonstrated the superiority of one product over others for all patients and all warts. Most patients will require a course of therapy vs. a single treatment. Most warts will typically respond to therapy in 3 months, but if response does not occur, then treatment options should be reassessed and modified if needed. The CDC recommended patient-applied regimens include: imiquimod 3.75% cream or 5% cream, podofilox 0.5% solution or gel, or Veregen.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Veregen. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Veregen is recommended in those who meet the following criteria:

FDA-Approved Indication

21. Genital or Perianal Warts, External. Approve for 4 months if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient is immunocompetent, according to the prescriber; AND
- **C)** Patient has tried BOTH of the following treatments (i and ii):
  - **i.** Podofilox gel or solution; AND
  - **ii.** Imiquimod cream.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Veregen is not recommended in the following situations:

103. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

124. Veregen® ointment [prescribing information]. Melville, NY: Fougera; November 2022.
125. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2021. *MMWR*. 2021;70(4):1-192.

PRIOR AUTHORIZATION POLICY

POLICY: Vesicular Monoamine Transporter Type 2 Inhibitors – Austedo Prior Authorization Policy
- Austedo® (deutetrabenazine tablets – Teva)
- Austedo® XR (deutetrabenazine extended-release tablets – Teva)

REVIEW DATE: 04/26/2023

OVERVIEW

Austedo and Austedo XR, vesicular monoamine transporter type 2 inhibitors, are indicated in adults for the following uses:[1]
- **Chorea associated with Huntington's disease**.
- **Tardive dyskinesia**.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Austedo/Austedo XR. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Austedo/Austedo XR as well as the monitoring required for adverse events and long-term efficacy, approval requires Austedo/Austedo XR to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Austedo/Austedo XR is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Chorea Associated with Huntington's Disease.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Diagnosis of Huntington's disease is confirmed by genetic testing (for example, an expanded HTT CAG repeat sequence of at least 36); AND
   - **C)** The medication is prescribed by or in consultation with a neurologist.

2. **Tardive dyskinesia.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** The medication is prescribed by or in consultation with a neurologist or psychiatrist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Austedo/Austedo XR is not recommended in the following situations:

25. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

236. Austedo® tablets/Austedo® XR extended-release tablets [prescribing information]. North Wales, PA: Teva; February 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Vesicular Monoamine Transporter Type 2 Inhibitors – Ingrezza Prior Authorization Policy
- Ingrezza® (valbenazine capsules – Neurocrine Biosciences)

REVIEW DATE: 06/07/2023, selected revision 8/30/2023

OVERVIEW

Ingrezza, a vesicular monoamine transporter type 2 inhibitor, is indicated in adults for the treatment of the following uses:[1]

- **Chorea associated with Huntington's disease.**
- **Tardive dyskinesia.**

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ingrezza. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ingrezza as well as the monitoring required for adverse events and long-term efficacy, approval requires Ingrezza to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ingrezza is recommended in those who meet one of the following criteria:

FDA-Approved Indications

3. Chorea Associated with Huntington's Disease. Approve for 1 year if the patient meets the following (A, B, and C):
- **D)** Patient is ≥ 18 years of age; AND
- **E)** Diagnosis of Huntington's disease is confirmed by genetic testing (for example, an expanded HTT CAG repeat sequence of at least 36); AND
- **F)** The medication is prescribed by or in consultation with a neurologist.

4. Tardive Dyskinesia. Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The medication is prescribed by or in consultation with a neurologist or psychiatrist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ingrezza is not recommended in the following situations:

26. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

237. Ingrezza® capsules [prescribing information]. San Diego, CA: Neurocrine Biosciences; August 2023.

PRIOR AUTHORIZATION POLICY

POLICY: Vesicular Monoamine Transporter Type 2 Inhibitors – Tetrabenazine Prior Authorization Policy

- Xenazine® (tetrabenazine tablets – Lundbeck, generic)

REVIEW DATE: 06/07/2023

OVERVIEW

Tetrabenazine, a vesicular monoamine transporter type 2 inhibitor, is indicated for the treatment of **chorea associated with Huntington's disease** in adults.[1]

Clinical Efficacy

There are several published studies which have assessed the efficacy and safety of tetrabenazine for the treatment of other hyperkinetic movement disorders (e.g., tics in Tourette syndrome and tardive dyskinesia).[2-4] While most of the data for treatment of Tourette syndrome indicate that antipsychotic medications, both typical and atypical, are most effective, other medications (including tetrabenazine) may be used first to avoid the potential side effects of dopamine blockade.[5]

Guidelines

The American Academy of Neurology (AAN) evidence-based guidelines on pharmacologic treatment of chorea in Huntington's disease (2012) state that if chorea in Huntington's disease requires treatment, clinicians should prescribe tetrabenazine, amantadine, or Rilutek® (riluzole tablets) [Level B].[6]

The AAN published an evidence-based guideline for the treatment of tardive syndromes (2013).[7] The authors found that tetrabenazine possibly reduces tardive syndrome symptoms (based on two consistent Class III studies). Therefore, tetrabenazine may be considered in treating tardive syndromes (Level C).

The AAN published practice guideline recommendations for the treatment of tics in patients with Tourette syndrome and chronic tic disorders (2019).[8] The guidelines state that the dopamine depleters, tetrabenazine, deutetrabenazine, and valbenazine, are lacking published, randomized, controlled trials in the treatment of tics but note that these drugs are increasingly used off-label. When appropriately dosed, these drugs are generally well-tolerated but may be associated with drowsiness, depression, and parkinsonism.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of tetrabenazine. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with tetrabenazine as well as the monitoring required for adverse events and long-term efficacy, approval requires tetrabenazine to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of tetrabenazine is recommended in those who meet one of the following criteria:

FDA-Approved Indication

5. **Chorea Associated with Huntington's Disease.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   C) Patient is ≥ 18 years of age; AND
19. Diagnosis of Huntington's disease is confirmed by genetic testing (for example, an expanded HTT CAG repeat sequence of at least 36); AND
20. The medication is prescribed by or in consultation with a neurologist.

Other Uses with Supportive Evidence

6. **Hyperkinetic Dystonia.** Approve for 1 year if the patient meets the following criteria (A and B):
   1. Patient is ≥ 18 years of age; AND
   2. The medication is prescribed by or in consultation with a neurologist.

7. **Tardive Dyskinesia.** Approve for 1 year if the patient meets the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) The medication is prescribed by or in consultation with a neurologist or psychiatrist.

8. **Tourette Syndrome and Related Tic Disorders.** Approve for 1 year if the patient meets the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) The medication is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of tetrabenazine is not recommended in the following situations:

27. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

238. Xenazine® tablets [prescribing information]. Deerfield, IL: Lundbeck; September 2017.
239. Merative Micromedex®. Merative US. Available at: https://www.micromedexsolutions.com/. Accessed on June 3, 2023. Search terms: tetrabenazine.
240. Chen JJ, Ondo WG, Dashtipour K, et al. Tetrabenazine for the treatment of hyperkinetic movement disorders: a review of the literature. *Clin Ther*. 2012;34(7):1487-504.
241. Guay DR. Tetrabenazine, a monoamine-depleting drug used in the treatment of hyperkinetic movement disorders. *Am J Geriatr Pharmacother*. 2010;8(4):331-373.
242. Quezada J, Coffman KA. Current Approaches and New Developments in the Pharmacological Management of Tourette Syndrome. *CNS Drugs*. 2018; 32(1):33–45.
243. Armstrong MJ, Miyasaki JM. Evidence-based guideline: pharmacologic treatment of chorea in Huntington disease: report of the guideline development subcommittee of the American Academy of Neurology. *Neurology*. 2012;79:597-603.
244. Bhidayasiri R, Fahn S, Weiner WJ, et al. Evidence-based guideline: treatment of tardive syndromes: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2013;81(5):463-469.
245. Pringsheim T, Okun MS, Müller-Vahl K, et al. Practice guideline recommendations summary: treatment of tics in people with Tourette syndrome and chronic tic disorders. *Neurology*. 2019;92:896-906.

PRIOR AUTHORIZATION POLICY

POLICY: Vijoice Prior Authorization Policy
- Vijoice® (alpelisib tablets – Novartis)

REVIEW DATE: 05/10/2023

OVERVIEW
Vijoice, a kinase inhibitor, is indicated for the treatment of adults and pediatric patients ≥ 2 years of age with severe manifestations of phosphatidylinositol- 4,5-bisphosphate 3-kinase catalytic subunit alpha **(PIK3CA)-Related Overgrowth Spectrum** (PROS) who require systemic therapy.[1]

This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Disease Overview
PROS is a heterogeneous group of diseases caused by mutations in *PI3KCA* and characterized by a range of clinical features.[2] Examples of PROS include patients with congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal (CLOVES) syndrome; megalencephaly-capillary malformation (MCAP) syndrome; Klippel-Trenaunay syndrome (KTS); facial infiltrating lipomatosis (FIL); dysplastic megalencephaly (DMEG); hemimegalencephaly (HMEG); focal cortical dysplasia (FCD); or capillary vascular malformation of the lower lip, lymphatic malformations of the head and neck, asymmetry and partial or generalized overgrowth (CLAPO) syndrome.[2,3] The core features are congenital or early-childhood onset of segmental/focal overgrowth, predominantly affecting the brain, limbs (including fingers and toes), trunk (including abdomen and chest), and face, all usually in an asymmetric distribution. PROS-related complications can include hemorrhages; embolisms; vascular or lymphatic anomalies; congenital neurological complications; developmental delays; functional impairments; organ abnormalities, including cardiac and renal; superficial infections; chronic pain; skeletal anomalies; and psychological impact.[3] The diagnosis of PROS is often suspected by clinical features of the syndrome and can be confirmed with genetic testing of the *PI3KCA* gene.[2] Review articles state that management of PROS includes treatment of the manifestations, such as surgery, laser therapy, sclerotherapy, or oral medications such as sirolimus.[2,3,6]

Clinical Efficacy
The efficacy of Vijoice was evaluated in one single-arm pivotal study in patients who were treated as part of an expanded access program for compassionate use.[1,3] Eligible patients with PROS were ≥ 2 years of age, had severe or life-threatening clinical manifestations of PROS necessitating systemic treatment, and had documented evidence of mutation in the *PIK3CA* gene as determined by a local laboratory. The efficacy of Vijoice was evaluated in a total of 37 patients with at least one target lesion identified on imaging. The major efficacy outcome measure for the study was the proportion of patients with radiological response at Week 24, defined as a ≥ 20% reduction from baseline in the sum of measurable target lesion volume (1 to 3 lesions), in the absence of a ≥ 20% increase from baseline in any target lesion, progression of non-target lesions, or appearance of a new lesion. This trial demonstrated that the response rate of Vijoice was 27% (10 out of 37 patients) and the proportion of patients with duration of response ≥ 6 months was 70% (60% of patients had duration of response ≥ 12 months)[1,3] Clinically meaningful improvement in PROS-related signs and symptoms (e.g., pain, fatigue, vascular malformation, limb asymmetry, or disseminated intravascular coagulation) were observed.[3]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Vijoice. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Vijoice is recommended in those who meet the following criteria:

FDA-Approved Indication

21. PIK3CA-Related Overgrowth Spectrum (PROS). Approve for the duration noted if the patient meets ONE of the following criteria (A or B):
Note: Examples of PROS include congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal (CLOVES) syndrome; megalencephaly-capillary malformation (MCAP) syndrome; Klippel-Trenaunay syndrome (KTS); facial infiltrating lipomatosis (FIL), dysplastic megalencephaly (DMEG); hemimegalencephaly (HMEG); focal cortical dysplasia (FCD); or capillary vascular malformation of the lower lip, lymphatic malformations of the head and neck, asymmetry and partial or generalized overgrowth (CLAPO) syndrome.

H) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, and iv):
- **i.** Patient is ≥ 2 years of age; AND
- **ii.** Patient has at least one severe clinical manifestation of PROS, as determined by the prescriber; AND
  Note: Examples of severe clinical manifestations include excessive tissue growth, blood vessel malformations, scoliosis, vascular tumors, cardiac or renal manifestations, and those who require systemic treatment.
- **iii.** Patient has a *PIK3CA* mutation as confirmed by genetic testing; AND
- **iv.** The medication is being prescribed by or in consultation with a physician that specializes in treatment of genetic disorders.

I) Patient is Currently Receiving Vijoice. Approve for 1 year if the patient meets the following criteria (i, ii and ii):
- **i.** Patient has been established on Vijoice for at least 6 months; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy with Vijoice is reviewed under criterion A (Initial Therapy).
- **ii.** Patient has experienced a reduction in volume from baseline (prior to initiating Vijoice) in at least one lesion, as confirmed by measurement; AND
- **iii.** Patient has experienced an improvement in at least one sign or symptom of PROS from baseline (prior to initiating Vijoice).
  Note: Examples of signs or symptoms of PROS include pain, fatigue, vascular malformation, limb asymmetry, or disseminated intravascular coagulation.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vijoice is not recommended in the following situations:

10. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

34. Vijoice® tablets [prescribing information]. East Hanover, NJ: Novartis; November 2022.
35. Mirzaa G, Graham JM Jr, Keppler-Noreuil K. PIK3CA-related overgrowth spectrum. 2013 Aug 15 [Updated 2021 Dec 23]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. Gene Reviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022.
36. Canaud G, Lopez Gutierrez JC, Irvine A, et al. EPIK-P1: retrospective chart review study of patients with PIK3CA-related overgrowth spectrum who have received alpelisib as part of a compassionate use programme [abstract]. Presented at: The 2021 European Society for Medical Oncology (ESMO) Congress; virtual; September 16-21, 2021.
37. Keppler-Noreuil K, Rios JJ, Parker V, et al. PIK3CA-related overgrowth spectrum (PROS): diagnostic and testing eligibility criteria, differential diagnosis, and evaluation. *Am J Med Genet A*. 2015;0(2):287-295.
38. National Center of Advancing Translational Sciences. Genetic and Rare Disease Information Center. PIK3CA-related overgrowth spectrum. Available at: https://rarediseases.info.nih.gov/diseases/12182/pik3ca-related-overgrowth-spectrum. Created January 29, 2018. Accessed on May 8, 2023.
39. Canuad G, Hammil AM, Adams D. A review of mechanisms of disease across PIK3CA-related disorders with vascular manifestations. *Orphanet J Rare Dis*. 2021;16(1):306.

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PRIOR AUTHORIZATION WITH STEP THERAPY POLICY

POLICY: Wakefulness-Promoting Agents – Armodafinil, Modafinil Prior Authorization with Step Therapy Policy
- Nuvigil® (armodafinil tablets – Cephalon, generic)
- Provigil® (modafinil tablets – Cephalon, generic)

REVIEW DATE: 09/20/2023

OVERVIEW

Armodafinil and modafinil, agents with wake-promoting actions that are similar to sympathomimetic agents (e.g., amphetamine and methylphenidate), are indicated to improve wakefulness in adults with **excessive sleepiness** associated with the following conditions:[1,2]
- **Narcolepsy**.
- **Obstructive sleep apnea/hypoapnea syndrome** (approved as adjunctive therapy).
- **Shift work sleep disorder**.

Armodafinil and modafinil are Schedule IV controlled substances.[1,2] Review of the medical literature notes many other uses of modafinil that are considered off-label or investigational. While armodafinil has not been studied off-label to the same extent as modafinil, it is expected that armodafinil will have similar clinical efficacy for these uses. Additionally, in the pivotal trials for shift work sleep disorder, enrolled patients were required to work a minimum of five night shifts per month.

Two specialized tests, which can be performed in a sleep disorders clinic, are required to establish a diagnosis of narcolepsy.[3] Polysomnogram (PSG) is an overnight recording of brain and muscle activity, breathing, and eye movements. The multiple sleep latency test assesses daytime sleepiness by measuring how quickly a person falls asleep and whether they enter rapid eye movement (REM) sleep. On the day after PSG, the patient is asked to take five short naps separated by two hours over the course of a day. If an individual falls asleep in < 8 minutes on average over the five naps, this indicates excessive daytime sleepiness. However, patients with narcolepsy also have an abnormally quick start to REM sleep. If REM sleep happens within 15 minutes at least two times out of the five naps and the sleep study the night before, this is likely an abnormality caused by narcolepsy.

Guidelines

Pertinent medical guidelines related to modafinil and armodafinil are summarized below.

Narcolepsy and Cataplexy

The American Academy of Sleep Medicine (AASM) practice parameters for the treatment of central disorders of hypersomnolence were updated in 2021.[4,5]
- Modafinil, Wakix® (pitolisant tablets), Xyrem® (sodium oxybate oral solution), and Sunosi™ (solriamfetol tablets) are recommended as effective treatments for daytime sleepiness due to narcolepsy and reducing disease severity in adults (Strong Recommendation for each).
- Wakix and Xyrem have also demonstrated efficacy for the treatment of cataplexy in patients with narcolepsy (Strong Recommendation for each).
- Xyrem and armodafinil have Conditional Recommendations for the treatment of narcolepsy, showing efficacy for daytime sleepiness due to narcolepsy and reducing disease severity.
- Dextroamphetamine has a Conditional Recommendation for the treatment of narcolepsy, showing efficacy for excessive daytime sleepiness and cataplexy.

- Methylphenidate has a Conditional Recommendation for the treatment of narcolepsy, showing efficacy in reducing disease severity.
- There was insufficient and inconclusive evidence to make recommendations for l-carnitine, scheduled naps, selegiline, triazolam, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs).
- Modafinil and Xyrem have Conditional Recommendations for the treatment of narcolepsy in pediatric patients.
- A Strong Recommendation should be followed by clinicians under most circumstances. A Conditional Recommendation requires that the clinician use clinical knowledge and experience and strongly consider the individual patient's values and preferences to determine the best course of action.

Excessive Daytime Sleepiness Associated with Obstructive Sleep Apnea/Hypoapnea Syndrome

- According to the AASM guideline on medical therapy for obstructive sleep apnea (OSA) [2006], continuous positive airway pressure (CPAP) is the most uniformly effective therapy, and, to date, this is the only intervention for OSA shown to have favorable impacts on both cardiovascular and neurobehavioral morbidities.[6]
- Modafinil, in patients compliant with nasal CPAP, consistently improved subjective and objective sleepiness, quality of life, and vigilance compared with placebo.

Adjunctive/Augmentation Treatment for Major Depressive Disorder

- According to the American Psychiatric Association (APA) practice guideline for the treatment of patients with major depressive disorder (2010), modafinil (or methylphenidate) are potential treatments for sedation associated with antidepressant medications.[7]
- The APA guidelines state that modafinil has shown benefit when combined with an SSRI, related to specific effects on residual symptoms such as fatigue and hypersomnolence.
- The guidelines note that there is no clear guidance regarding the length of time modafinil should be co-administered.
- While armodafinil has not been studied for this use, it is considered to be interchangeable with modafinil for this condition.

Excessive Daytime Sleepiness Associated with Myotonic Dystrophy

- Practice parameters from the AASM, last updated in 2021, suggest that clinicians use modafinil for the treatment of hypersomnia secondary to myotonic dystrophy in adults (Conditional Recommendation).[4,5]
- While armodafinil has not been studied for this use, it is considered to be interchangeable with modafinil for this condition.

Excessive Daytime Sleepiness Associated with Parkinson's Disease

- Practice parameters from the AASM (2021) suggest that clinicians use modafinil for the treatment of hypersomnia secondary to Parkinson's disease in adults (Conditional Recommendation).[4,5]
- While armodafinil has not been studied for this use, it is considered to be interchangeable with modafinil for this condition.

Fatigue Associated with Multiple Sclerosis

- Practice parameters from the AASM (2021) suggest that clinicians use modafinil for the treatment of hypersomnia secondary to multiple sclerosis in adults (Conditional Recommendation).[4,5]
- While armodafinil has not been studied for this use, expert opinion considers it to be interchangeable with modafinil for this condition.

Idiopathic Hypersomnia
Idiopathic hypersomnia, a condition similar to narcolepsy, is characterized by constant or recurrent daytime sleepiness with no other cause of sleepiness, prolonged nocturnal sleep, difficulty awakening with sleep drunkenness, and long unrefreshing naps with no of cataplexy.[8-10] The AASM practice parameters for the treatment of central disorders of hypersomnolence (2021) include recommendations for the treatment of idiopathic hypersomnia.[4,5]

- Only modafinil has a Strong Recommendation for use.
- Clarithromycin, methylphenidate, Wakix, and Xyrem have Conditional Recommendations for the treatment of idiopathic hypersomnia in adults.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of modafinil (brand and generic) and armodafinil (brand and generic). This Prior Authorization Policy also contains a Step Therapy component. When clinically appropriate, the patient is directed to try one Step 1 Product (generic modafinil or generic armodafinil) prior to brand Nuvigil or brand Provigil (Step 2). All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of modafinil (brand and generic) and armodafinil (brand and generic) is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Excessive Daytime Sleepiness Associated with Narcolepsy.** Approve for 1 year if the patient meets the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has been evaluated using polysomnography and a multiple sleep latency test; AND
   - **C)** Diagnosis of narcolepsy has been confirmed, according to the prescriber; AND
   - **D)** The medication is prescribed by or in consultation with a sleep specialist physician or a neurologist; AND
   - **E)** If brand Provigil or Nuvigil is being requested, the patient meets both of the following (i and ii):
   - **iii.** Patient has tried generic modafinil or generic armodafinil; AND
   - **iv.** Brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

2. **Excessive Daytime Sleepiness Associated with Obstructive Sleep Apnea/Hypoapnea Syndrome.** Approve for 1 year if the patient meets the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets one of the following (i or ii):
   - **i.** Armodafinil/modafinil will be used in conjunction with continuous positive airway pressure therapy; OR
   - **ii.** Patient is unable to initiate or tolerate continuous positive airway pressure therapy; AND
   - **C)** If brand Provigil or Nuvigil is being requested, the patient meets both of the following (i and ii):

i. Patient has tried generic modafinil or generic armodafinil; AND

ii. Brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

3. **Excessive Sleepiness Associated with Shift Work Sleep Disorder.** Approve for 1 year if the patient meets the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient works at least five overnight shifts per month; AND
   C) If brand Provigil or Nuvigil is being requested, the patient meets both of the following (i and ii):
      i. Patient has tried generic modafinil or generic armodafinil; AND
      ii. Brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

Other Uses with Supportive Evidence

4. **Adjunctive/Augmentation Treatment for Depression in Adults.** Approve for 1 year if the patient meets the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient is concurrently receiving other medication therapy for depression; AND
   Note: Examples of other medications for the treatment of depression include selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs).
   C) If brand Provigil or Nuvigil is being requested, the patient meets both of the following (i and ii):
   i. Patient has tried generic modafinil or generic armodafinil; AND
   ii. Brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

5. **Excessive Daytime Sleepiness Associated with Myotonic Dystrophy.** Approve for 1 year if the patient meets both of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) If brand Provigil or Nuvigil is being requested, the patient meets both of the following (i and ii):
   i. Patient has tried generic modafinil or generic armodafinil; AND
   ii. Brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

6. **Excessive Daytime Sleepiness Associated with Parkinson's Disease.** Approve for 1 year if the patient meets both of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) If brand Provigil or Nuvigil is being requested, the patient meets both of the following (i and ii):
   i. Patient has tried generic modafinil or generic armodafinil; AND
   ii. Brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the

corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

7. **Fatigue Associated with Multiple Sclerosis.** Approve for 1 year if the patient meets both of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) If brand Provigil or Nuvigil is being requested, the patient meets both of the following (i and ii):
      i. Patient has tried generic modafinil or generic armodafinil; AND
      ii. Brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

8. **Idiopathic Hypersomnia.** Approve for 1 year if the patient meets the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) The diagnosis is confirmed by a sleep specialist physician or at an institution that specializes in sleep disorders (i.e., sleep center); AND
   C) If brand Provigil or Nuvigil is being requested, the patient meets both of the following (i and ii):
      i. Patient has tried generic modafinil or generic armodafinil; AND
      ii. Brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of modafinil (brand and generic) and armodafinil (brand and generic) is not recommended in the following situations:

4. **Attention Deficit Hyperactivity Disorder (ADHD).** The American Academy of Pediatrics clinical practice guidelines for the treatment of ADHD in children and adolescents (2011 and 2019) do not address the use of modafinil/armodafinil.[11,12] These guidelines note that with the greater availability of approved medications for children/adolescents with ADHD, it has become increasingly unlikely that clinicians need to consider the off-label use of other medications. Many options exist for the treatment of ADHD in adults (e.g., methylphenidate, dextroamphetamine) and further large scale trials that demonstrate benefit for modafinil in adults with ADHD are needed.

5. **Bipolar Disorder, including Bipolar Depression.** Limited data (one small study [n = 85] and case reports [n = 2]) are available that describe the use of modafinil for bipolar disorder and bipolar depression.[13-15] In one study (n = 257), armodafinil was not more effective than placebo in treating bipolar depression.[16] Only limited data support modafinil for this condition and more data are needed.

6. **Cancer-Related Fatigue.** The National Comprehensive Cancer Network guidelines on cancer-related fatigue (version 2.2023 – January 30, 2023) no longer consider modafinil or armodafinil to be effective for the treatment of cancer-related fatigue and recommend against its use.[17]

7. **Chronic Fatigue Syndrome.** Limited data characterize modafinil therapy in those with chronic fatigue syndrome.[18] In a randomized, double-blind, crossover study in 14 patients with chronic fatigue syndrome, use of modafinil for 20 days had minimal effects on cognitive function and no significant

effects on fatigue, health-related quality of life, or mood.[19] More data are required to assess efficacy in this patient population.

8. **Excessive Daytime Sleepiness Associated with Primary Insomnia.** One randomized, placebo-controlled study found that neither combination therapy with modafinil and cognitive behavioral therapy nor modafinil as monotherapy significantly decreased daytime sleepiness associated with primary insomnia.[20]

9. **Enhancement of Performance in Situations of Induced Sleep Deprivation.** Studies are needed to define the role/appropriateness of modafinil in these situations for the general population (as opposed to military personnel, etc.). Studies have shown that modafinil may enhance performance and sustain alertness in individuals subjected to situations that deprive sleep (e.g., military aviation, emergency physicians).[21-24] Further studies are needed before its use in the general population in these types of situations can be promoted.

10. **Fibromyalgia.** Limited data are available regarding the use of modafinil in fibromyalgia with most of the data being observational.[25-27] Larger-sized, randomized, placebo-controlled trials are required to better assess and validate the efficacy of modafinil in patients with fibromyalgia before it can be recommended as a therapeutic modality.

11. **Hypersomnia, Fatigue or Sleepiness Due to Other Conditions (not Idiopathic Hypersomnia, see Other Uses with Supportive Evidence).** More data are needed in specific conditions to define the role of modafinil and armodafinil.

12. **Post-Stroke Sleep-Wake Disorders or Sleep Disorders.** Sleep-wake disorders occur in approximately 20% to 40% of patients who have experienced a stroke, which includes hypersomnia and excessive daytime sleepiness. Very limited data (i.e., case reports and one small study) have explored the use of modafinil in these patients to improve alertness.[28,29] More data are needed to determine effectiveness in this condition.

13. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION WITH STEP THERAPY POLICY

POLICY: Wakefulness-Promoting Agents – Sunosi Prior Authorization with Step Therapy Policy
- Sunosi® (solriamfetol tablets – Jazz)

REVIEW DATE: 09/20/2023

OVERVIEW

Sunosi, a dopamine and norepinephrine reuptake inhibitor, is indicated to improve wakefulness in adults with **excessive daytime sleepiness** associated with the following conditions:[1]

- **Narcolepsy**.
- **Obstructive sleep apnea** (OSA).
  Limitations of Use: Sunosi is not indicated to treat the underlying airway obstruction in OSA.[1] The underlying airway obstruction should be treated (e.g., with continuous positive airway pressure [CPAP]) for at least 1 month prior to initiating Sunosi for excessive daytime sleepiness. Modalities to treat the underlying airway obstruction should be continued during treatment with Sunosi.

Sunosi is a Schedule IV controlled substance.[1]

Armodafinil and modafinil are wakefulness-promoting agents with actions similar to sympathomimetic agents (e.g., amphetamine and methylphenidate).[2,3] They are indicated to improve wakefulness in adults with excessive sleepiness associated with narcolepsy, OSA, or shift work disorder. Armodafinil and modafinil are Schedule IV controlled substances. Stimulant medications (e.g., amphetamine, methamphetamine, dextroamphetamine, and methylphenidate) are used off-label for the treatment of daytime sleepiness due to narcolepsy and OSA and are mentioned in guidelines.[4-7]

Two specialized tests, which can be performed in a sleep disorders clinic, are required to establish a diagnosis of narcolepsy.[8] Polysomnogram (PSG) is an overnight recording of brain and muscle activity, breathing, and eye movements. The multiple sleep latency test assesses daytime sleepiness by measuring how quickly a person falls asleep and whether they enter rapid eye movement (REM) sleep. On the day after PSG, the patient is asked to take five short naps separated by two hours over the course of a day. If an individual falls asleep in < 8 minutes on average over the five naps, this indicates excessive daytime sleepiness. However, patients with narcolepsy also have an abnormally quick start to REM sleep. If REM sleep happens within 15 minutes at least two times out of the five naps and the sleep study the night before, this is likely an abnormality caused by narcolepsy.

Guidelines

Narcolepsy and Cataplexy

The American Academy of Sleep Medicine (AASM) practice parameters for the treatment of central disorders of hypersomnolence were updated in 2021.[4,5]

- Modafinil, Wakix® (pitolisant tablet), Xyrem® (sodium oxybate oral solution), and Sunosi are recommended as effective treatments for daytime sleepiness due to narcolepsy and reducing disease severity in adults (Strong Recommendation for each).
- Wakix and Xyrem have also demonstrated efficacy for the treatment of cataplexy in patients with narcolepsy (Strong Recommendation for each).
- Xyrem and armodafinil have Conditional Recommendations for the treatment of narcolepsy, showing efficacy for daytime sleepiness due to narcolepsy and reducing disease severity.

- Dextroamphetamine has a Conditional Recommendation for the treatment of narcolepsy, showing efficacy for excessive daytime sleepiness and cataplexy.
- Methylphenidate has a Conditional Recommendation for the treatment of narcolepsy, showing efficacy in reducing disease severity.
- There was insufficient and inconclusive evidence to make recommendations for l-carnitine, scheduled naps, selegiline, triazolam, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs).
- Modafinil and Xyrem have Conditional Recommendations for the treatment of narcolepsy in pediatric patients.
- A Strong Recommendation should be followed by clinicians under most circumstances. A Conditional Recommendation requires that the clinician use clinical knowledge and experience and strongly consider the individual patient's values and preferences to determine the best course of action.

Excessive Daytime Sleepiness Associated with Obstructive Sleep Apnea/Hypoapnea Syndrome

- According to the AASM guideline on medical therapy for OSA (2006), CPAP is the most uniformly effective therapy, and, to date, this is the only intervention for OSA shown to have favorable impacts on both cardiovascular and neurobehavioral morbidities.[6,7]
- Modafinil, in patients compliant with nasal CPAP, consistently improved subjective and objective sleepiness, quality of life, and vigilance compared with placebo.
- Sunosi is not addressed in these guidelines.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Sunosi. This Prior Authorization Policy also contains a Step Therapy component. When clinically appropriate, the patient is directed to try one Step 1 Product (modafinil or armodafinil) prior to Sunosi (Step 2). All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sunosi is recommended in those who meet one of the following criteria:

FDA-Approved Indications

22. Excessive Daytime Sleepiness Associated with Narcolepsy. Approve for 1 year if the patient meets the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has been evaluated using polysomnography and a multiple sleep latency test; AND
- **C)** Diagnosis of narcolepsy has been confirmed, according to the prescriber; AND
- **D)** The medication is prescribed by or in consultation with a sleep specialist physician or a neurologist; AND
- **E)** Patient has tried generic modafinil or generic armodafinil.
  Note: An exception to this requirement is allowed if the patient has previously tried brand Provigil or brand Nuvigil.

2. **Excessive Daytime Sleepiness Associated with Obstructive Sleep Apnea.** Approve for 1 year if the patient meets the following (A, B, and C):
   - **D)** Patient is ≥ 18 years of age; AND
   - **E)** Patient meets one of the following (i or ii):
   - **i.** Sunosi will be used in conjunction with continuous positive airway pressure (CPAP) therapy; OR
   - **ii.** Patient is unable to initiate or tolerate CPAP therapy; AND
   - **F)** Patient has tried generic modafinil or generic armodafinil.

   Note: An exception to this requirement is allowed if the patient has previously tried brand Provigil or brand Nuvigil.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sunosi is not recommended in the following situations:

104. Concomitant Use of Sunosi with an Oxybate Product and/or Wakix (pitolisant tablets). Sunosi, a dopamine and norepinephrine reuptake inhibitor, is indicated to improve wakefulness in adults with excessive daytime sleepiness due to narcolepsy or obstructive sleep apnea.[1] Oxybate products include Xyrem (sodium oxybate oral solution), Lumryz (sodium oxybate extended-release oral suspension), and Xywav (calcium, magnesium, potassium, and sodium oxybates oral solution).[10-12] These have the same active ingredient (oxybate, a central nervous system depressant) and have not been studied for use in combination or as alternating treatments. Wakix, an antagonist/inverse agonist of the histamine-3 receptor, is indicated for excessive daytime sleepiness and cataplexy in adults with narcolepsy.[13] Currently, there are no published studies evaluating combination use of these medications.

105. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION WITH STEP THERAPY POLICY

POLICY: Wakefulness-Promoting Agents – Wakix Prior Authorization with Step Therapy Policy
- Wakix® (pitolisant tablets – Harmony)

REVIEW DATE: 09/20/2023

OVERVIEW

Wakix, an antagonist/inverse agonist of the histamine-3 receptor, is indicated for the following uses:[1]
- **Excessive daytime sleepiness in adults with narcolepsy**.
- **Cataplexy in adults with narcolepsy**.

Wakix is the only wakefulness-promoting agent that is not a controlled substance.[1-4]

Armodafinil and modafinil are wakefulness-promoting agents with actions similar to sympathomimetic agents (e.g., amphetamine and methylphenidate).[2,3] They are indicated to improve wakefulness in adults with excessive sleepiness associated with narcolepsy, obstructive sleep apnea (OSA), or shift work disorder. Sunosi® (solriamfetol tablets), a dopamine and norepinephrine reuptake inhibitor, is indicated to improve wakefulness in adults with excessive daytime sleepiness associated with narcolepsy or OSA.[4] Armodafinil, modafinil, and Sunosi are Schedule IV controlled substances.[2-4] Armodafinil, modafinil, and Sunosi are not indicated for the treatment of cataplexy.

Two specialized tests, which can be performed in a sleep disorders clinic, are required to establish a diagnosis of narcolepsy.[7] Polysomnogram is an overnight recording of brain and muscle activity, breathing, and eye movements. The multiple sleep latency test assesses daytime sleepiness by measuring how quickly a person falls asleep and whether they enter rapid eye movement (REM) sleep. On the day after polysomnogram, the patient is asked to take five short naps separated by two hours over the course of a day. If an individual falls asleep in < 8 minutes on average over the five naps, this indicates excessive daytime sleepiness. However, patients with narcolepsy also have an abnormally quick start to REM sleep. If REM sleep happens within 15 minutes at least two times out of the five naps and the sleep study the night before, this is likely an abnormality caused by narcolepsy.

Guidelines

Narcolepsy and Cataplexy

The American Academy of Sleep Medicine (AASM) practice parameters for the treatment of central disorders of hypersomnolence were updated in 2021.[5,6]
- Modafinil, Wakix, Xyrem® (sodium oxybate oral solution), and Sunosi are recommended as effective treatments for daytime sleepiness due to narcolepsy and reducing disease severity in adults (Strong Recommendation for each).
- Wakix and Xyrem have also demonstrated efficacy for the treatment of cataplexy in patients with narcolepsy (Strong Recommendation for each).
- Xyrem and armodafinil have Conditional Recommendations for the treatment of narcolepsy, showing efficacy for daytime sleepiness due to narcolepsy and reducing disease severity.
- Dextroamphetamine has a Conditional Recommendation for the treatment of narcolepsy, showing efficacy for excessive daytime sleepiness and cataplexy.
- Methylphenidate has a Conditional Recommendation for the treatment of narcolepsy, showing efficacy in reducing disease severity.

- There was insufficient and inconclusive evidence to make recommendations for l-carnitine, scheduled naps, selegiline, triazolam, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors.
- Modafinil and Xyrem have Conditional Recommendations for the treatment of narcolepsy in pediatric patients.
- A Strong Recommendation should be followed by clinicians under most circumstances. A Conditional Recommendation requires that the clinician use clinical knowledge and experience and strongly consider the individual patient's values and preferences to determine the best course of action.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Wakix. This Prior Authorization Policy also contains a Step Therapy component. When clinically appropriate, the patient is directed to try one Step 1 Product (dextroamphetamine for cataplexy in narcolepsy; modafinil or armodafinil for excessive daytime sleepiness in narcolepsy) prior to Wakix (Step 2). All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Wakix is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Cataplexy Treatment in a Patient with Narcolepsy**. Approve for 1 year if the patient meets the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has been evaluated using polysomnography and a multiple sleep latency test; AND
   - **C)** Diagnosis of narcolepsy has been confirmed, according to the prescriber; AND
   - **D)** The medication is prescribed by or in consultation with a sleep specialist physician or a neurologist; AND
   - **E)** Patient meets ONE of the following (i or ii):
     - **i.** Patient has tried dextroamphetamine; OR
     - **ii.** Patient has a contraindication or intolerance to dextroamphetamine, according to the prescriber. Note: Contraindications to dextroamphetamine include a history of substance use disorder; advanced arteriosclerosis, symptomatic cardiovascular disease, and/or moderate to severe hypertension; hyperthyroidism; known hypersensitivity to sympathomimetic amines; glaucoma; agitated states; concomitant administration with monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs.

2. **Excessive Daytime Sleepiness Associated with Narcolepsy.** Approve for 1 year if the patient meets the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has been evaluated using polysomnography and a multiple sleep latency test; AND
   - **C)** Diagnosis of narcolepsy has been confirmed, according to the prescriber; AND
   - **D)** The medication is prescribed by or in consultation with a sleep specialist physician or a neurologist; AND
   - **E)** Patient meets one of the following (i or ii):
     - **i.** Patient has tried generic modafinil or generic armodafinil; OR

Note: An exception to this requirement is allowed if the patient has previously tried brand Provigil or brand Nuvigil.

ii. Patient has a of substance use disorder and a wakefulness-promoting agent that is not a controlled substance is necessary, per the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Wakix is not recommended in the following situations:

106. Concomitant Use of Wakix with an Oxybate Product and/or Sunosi (solriamfetol tablets). Wakix, an antagonist/inverse agonist of the histamine-3 receptor, is indicated for excessive daytime sleepiness and cataplexy in adults with narcolepsy.[1] Oxybate products include Xyrem (sodium oxybate oral solution), Lumryz (sodium oxybate extended-release oral suspension), and Xywav (calcium, magnesium, potassium, and sodium oxybates oral solution).[8-10] These products have the same active ingredient (oxybate, a central nervous system depressant) and have not been studied for use in combination or as alternating treatments. Sunosi, a dopamine and norepinephrine reuptake inhibitor, is indicated to improve wakefulness in adults with excessive daytime sleepiness due to narcolepsy or obstructive sleep apnea.[2] Currently, there are no published studies evaluating combination use of these medications.

107. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Weight Loss – Glucagon-Like Peptide-1 Agonists Prior Authorization Policy
- Saxenda® (liraglutide subcutaneous injection – Novo Nordisk)
- Wegovy® (semaglutide subcutaneous injection – Novo Nordisk)
- Zepbound™ (tirzepatide subcutaneous injection – Eli Lilly)

REVIEW DATE: 07/12/2023; selected revision 07/26/2023, 09/13/0223, and 11/15/2023

OVERVIEW

Saxenda, Wegovy, and Zepbound, are glucagon-like peptide-1 (GLP-1) receptor agonists; Zepbound is also a glucose-dependent insulinotropic polypeptide (GIP) receptor agonist.[1,2,9] These agents are indicated as an adjunct to a reduced-calorie diet and increased physical activity for **chronic weight management** in the following settings:[1,2,9]

- **Saxenda, Wegovy, and Zepbound:** Adults with an initial body mass index (BMI) ≥ 30 kg/m^2 (obese), or ≥ 27 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension[1,2,9], dyslipidemia[1,2,9], type 2 diabetes[1,2,9], obstructive sleep apnea[9], or cardiovascular disease[9]).
- **Saxenda:** Pediatric patients ≥ 12 years of age with body weight > 60 kg and an initial BMI corresponding to 30 kg/m^2 for adults (obese) by international cutoffs.[2]
- **Wegovy:** Pediatric patients ≥ 12 years of age with an initial BMI at the 95th percentile or greater for age and sex (obesity).[1]

Dosing

In the prescribing information for Saxenda, a recommended dose escalation schedule of 4 weeks is outlined.[2] If a patient does not tolerate an increased dose during dose escalation, consider delaying dose escalation for approximately one additional week. For adults, the recommended maintenance dose of Saxenda is 3 mg once daily (QD); discontinue Saxenda if the patient cannot tolerate the 3 mg dose. Additionally, for adults, the prescribing information states to evaluate the change in body weight 16 weeks after initiating Saxenda and discontinue Saxenda if the patient has not lost at least 4% of baseline body weight, since it is unlikely the patient will achieve and sustain clinically meaningful weight loss with continued treatment. For pediatric patients, the recommended maintenance dose of Saxenda is 3 mg QD. However, pediatric patients who do not tolerate 3 mg QD may have their maintenance dose reduced to 2.4 mg QD. Discontinue Saxenda if the patient cannot tolerate the 2.4 mg dose. Additionally, for pediatric patients, the prescribing information states to evaluate the change in BMI after 12 weeks on the maintenance dose and discontinue Saxenda if the patient has not had a reduction in BMI of at least 1% from baseline, since it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

In the prescribing information for Wegovy, a recommended dose escalation schedule of 16 weeks is outlined.[1] If a patient does not tolerate an increased dose during dose escalation, consider delaying dose escalation for 4 weeks. The maintenance dose of Wegovy is 2.4 mg (recommended) or 1.7 mg injected subcutaneously (SC) once weekly; consider treatment response and tolerability when selecting the maintenance dose. The 0.25 mg, 0.5 mg, and 1 mg once weekly doses are initiation and escalation doses and are not approved doses for chronic weight management. If a pediatric patient ≥ 12 to < 18 years of age does not tolerate the maintenance dose of 2.4 mg once weekly, the dose can be reduced to 1.7 mg once weekly. Discontinue Wegovy if the patient cannot tolerate the 1.7 mg dose.

In the prescribing information for Zepbound, the recommended starting dose is 2.5 mg injected SC once weekly.[9] The 2.5 mg dose is for treatment initiation and is not intended for chronic weight management. After 4 weeks, the dose can be increased to 5 mg SC once weekly. The dose can then be increased in 2.5 mg increments, after at least 4 weeks on the current dose. The recommended maintenance doses are 5 mg, 10 mg, or 15 mg SC once weekly. The treatment response and tolerability should be considered when selecting the maintenance dose. If a patient does not tolerate a maintenance dose, consider a lower maintenance dose. The maximum dose is 15 mg SC once weekly. The 5 mg, 10 mg, and 15 mg maintenance doses would be reached after Week 4, Week 12, and Week 20, respectively.

Guidelines

Guidelines from the American Gastroenterological Association on pharmacological interventions for adults with obesity (2022) state that in adults with obesity or overweight with weight-related complications, who have had an inadequate response to lifestyle interventions, it is recommended to add pharmacological agents to lifestyle interventions over continuing lifestyle interventions alone (strong recommendation, moderate quality evidence).[6] Wegovy and Saxenda are listed among the therapeutic options. It is also noted that given the magnitude of net benefit, Wegovy may be prioritized over other approved anti-obesity medications for the long-term treatment of obesity for most patients.

Guidelines from the Endocrine Society regarding pharmacological management of obesity (2015) recommend pharmacotherapy as adjunct to behavioral modification to reduce food intake and increase physical activity for patients with BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 in the presence of at least one comorbidity, such as hypertension, dyslipidemia, type 2 diabetes, or obstructive sleep apnea.[3] If a patient's response to a weight loss medication is deemed effective (weight loss $\geq 5\%$ of body weight at 3 months) and safe, it is recommended that the medication be continued. In clinical studies of Saxenda and semaglutide, eligible patients were required to have a prior unsuccessful dietary weight loss attempt. The American Diabetes Association also cites weight loss $\geq 5\%$ of body weight at 3 months as "effective"; when early response is insufficient (typically $< 5\%$ weight loss after 3 months), other therapies should be evaluated.[8]

Per American Association of Clinical Endocrinologists/American College of Endocrinology obesity guidelines (2016), pharmacotherapy for overweight and obesity should be used only as an adjunct to lifestyle therapy and not alone.[4] The addition of pharmacotherapy produces greater weight loss and weight-loss maintenance compared with lifestyle therapy alone. The concurrent initiation of lifestyle therapy and pharmacotherapy should be considered in patients with weight-related complications that can be ameliorated by weight loss. Pharmacotherapy should be offered to patients with obesity, when potential benefits outweigh the risks, for the chronic treatment of the disease. Short-term treatment (3 to 6 months) using weight-loss medications has not been demonstrated to produce longer-term health benefits and cannot be generally recommended based on scientific evidence.

Guidelines in Pediatric Obesity

Guidelines from the American Academy of Pediatrics on evaluation and treatment of children and adolescents with obesity (2023) note that pediatricians and other primary health care providers should offer adolescents ≥ 12 years of age with obesity (BMI $\geq 95^{th}$ percentile) weight loss pharmacotherapy, according to medication indications, risks, and benefits, as an adjunct to health behavior and lifestyle treatment.[7]

A 2017 Endocrine Society clinical practice guideline on pediatric obesity recommends that pharmacotherapy in combination with lifestyle modification be considered in obese children or adolescents only after failure of a formal program of intensive lifestyle (dietary, physical activity and behavioral) modification to limit weight gain or to ameliorate comorbidities.[5] The Endocrine Society recommends pharmacotherapy in overweight children and adolescents < 16 years of age only in the context of a clinical trial. Pharmacotherapy should be provided only by clinicians who are experienced in the use of anti-obesity

agents and aware of the potential for adverse events. These guidelines recommend limited use of pharmacotherapy because pediatric obesity should be managed preferably as a serious lifestyle condition with important lifelong consequences. The Endocrine Society defines overweight as BMI in at least the 85th percentile but less than the 95th percentile, and obesity as BMI in at least the 95th percentile for age and sex against routine endocrine studies, unless the height velocity is attenuated or inappropriate for the family background or stage of puberty.[5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Saxenda, Wegovy, and Zepbound. Of note, this policy targets Saxenda, Wegovy, and Zepbound; other glucagon-like peptide-1 agonists which do not carry an FDA-approved indication for weight loss are not targeted in this policy. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Saxenda is recommended in those who meet the following criteria:

FDA-Approved Indications

1. Weight Loss, Adult. Approve for the duration noted if the patient meets one of the following (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets the following (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Patient has engaged in a trial of behavioral modification and dietary restriction for at least 3 months; AND

iii. Patient meets one of the following (a or b):

a) At baseline patient had a BMI ≥ 30 kg/m^2; OR
Note: This refers to baseline prior to any glucagon-like peptide-1 (GLP-1) agonist (e.g., Saxenda, Wegovy) or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (e.g., Zepbound).

b) At baseline, patient had a BMI ≥ 27 kg/m^2 and at least one of the following weight-related comorbidities: hypertension, type 2 diabetes, dyslipidemia, obstructive sleep apnea, or cardiovascular disease; AND
Note: This refers to baseline prior to any glucagon-like peptide-1 (GLP-1) agonist (e.g., Saxenda, Wegovy) or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (e.g., Zepbound).

iv. Saxenda will be used concomitantly with behavioral modification and a reduced-calorie diet.

B) Patient is Continuing Therapy with Saxenda. Approve for 1 year if the patient meets the following (i, ii, iii, iv, and v):
Note: For a patient who has not completed 4 months of initial therapy, refer to Initial Therapy criteria above.

i. Patient is ≥ 18 years of age; AND

ii. Patient meets one of the following (a or b):

a) At baseline, patient had a BMI ≥ 30 kg/m^2; OR

Note: This refers to baseline prior to any glucagon-like peptide-1 (GLP-1) agonist (e.g., Saxenda, Wegovy) or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (e.g., Zepbound).

b) At baseline, patient had a BMI ≥ 27 kg/m^2 and at least one of the following weight-related comorbidities: hypertension, type 2 diabetes, dyslipidemia, obstructive sleep apnea, or cardiovascular disease; AND

Note: This refers to baseline prior to any glucagon-like peptide-1 (GLP-1) agonist (e.g., Saxenda, Wegovy) or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (e.g., Zepbound).

iii. Patient has lost ≥ 4% of baseline body weight; AND

Note: This refers to baseline prior to any glucagon-like peptide-1 (GLP-1) agonist (e.g., Saxenda, Wegovy) or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (e.g., Zepbound).

iv. Patient is able to tolerate a Saxenda maintenance dose of 3 mg once daily; AND

v. Saxenda will be used concomitantly with behavioral modification and a reduced-calorie diet.

2. Weight Loss, Pediatric. Approve for the duration noted if the patient meets one of the following (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets the following (i, ii, iii, and iv):

i. Patient is ≥ 12 years of age and < 18 years of age; AND

ii. Patient has engaged in a trial of behavioral modification and dietary restriction for at least 3 months; AND

iii. At baseline, patient had a BMI ≥ 95th percentile for age and sex; AND

Note: This refers to baseline prior to any glucagon-like peptide-1 (GLP-1) agonist (e.g., Saxenda, Wegovy) or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (e.g., Zepbound).

iv. Saxenda will be used concomitantly with behavioral modification and a reduced-calorie diet.

B) Patient is Continuing Therapy with Saxenda. Approve for 1 year if the patient meets the following (i, ii, iii, iv, and v):

Note: For a patient who has not completed 4 months of initial therapy, refer to Initial Therapy criteria above.

i. Patient is ≥ 12 years of age and < 18 years of age; AND

ii. At baseline), patient had a BMI ≥ 95th percentile for age and sex; AND

Note: This refers to baseline prior to any glucagon-like peptide-1 (GLP-1) agonist (e.g., Saxenda, Wegovy) or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (e.g., Zepbound).

iii. Patient has had a reduction in BMI of ≥ 1% from baseline; AND

Note: This refers to baseline prior to any glucagon-like peptide-1 (GLP-1) agonist (e.g., Saxenda, Wegovy) or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (e.g., Zepbound).

iv. Patient is able to tolerate a Saxenda maintenance dose of 2.4 mg once daily or 3 mg once daily; AND

v. Saxenda will be used concomitantly with behavioral modification and a reduced-calorie diet.

II. Coverage of Wegovy is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Weight Loss, Adult.** Approve for the duration noted if the patient meets one of the following (A or B):
   - **A)** Initial Therapy. Approve for 7 months if the patient meets the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has engaged in a trial of behavioral modification and dietary restriction for at least 3 months; AND
     - **iii.** Patient meets one of the following (a or b):
       - **a)** At baseline, patient had a BMI ≥ 30 kg/m^2; OR
         Note: This refers to baseline prior to any glucagon-like peptide-1 (GLP-1) agonist (e.g., Saxenda, Wegovy) or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (e.g., Zepbound).
       - **b)** At baseline, patient had a BMI ≥ 27 kg/m^2 and at least one of the following weight-related comorbidities: hypertension, type 2 diabetes, dyslipidemia, obstructive sleep apnea, or cardiovascular disease; AND
         Note: This refers to baseline prior to any glucagon-like peptide-1 (GLP-1) agonist (e.g., Saxenda, Wegovy) or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (e.g., Zepbound).
     - **iv.** Wegovy will be used concomitantly with behavioral modification and a reduced-calorie diet.
   - **B)** Patient is Continuing Therapy with Wegovy. Approve for the duration noted below if the patient meets the following (i, ii, iii, iv, and v):
     Note: For a patient who has not completed 7 months of initial therapy, refer to Initial Therapy criteria above.
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient meets one of the following (a or b):
       - **a)** At baseline, patient had a BMI ≥ 30 kg/m^2; OR
         Note: This refers to baseline prior to any glucagon-like peptide-1 (GLP-1) agonist (e.g., Saxenda, Wegovy) or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (e.g., Zepbound).
       - **b)** At baseline, patient had a BMI ≥ 27 kg/m^2 and at least one of the following weight-related comorbidities: hypertension, type 2 diabetes, dyslipidemia, obstructive sleep apnea, or cardiovascular disease; AND
         Note: This refers to baseline prior to any glucagon-like peptide-1 (GLP-1) agonist (e.g., Saxenda, Wegovy) or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (e.g., Zepbound).
     - **iii.** Patient has lost ≥ 5% of baseline body weight; AND
       Note: This refers to baseline prior to any glucagon-like peptide-1 (GLP-1) agonist (e.g., Saxenda, Wegovy) or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (e.g., Zepbound).
     - **iv.** Wegovy will be used concomitantly with behavioral modification and a reduced-calorie diet; AND
     - **v.** Patient meets one of the following (a or b):
       - **a)** Patient is able to tolerate a Wegovy maintenance dose of 1.7 mg once weekly or 2.4 mg once weekly: Approve for 1 year; OR
       - **b)** Approve for up to 5 months if the patient meets both of the following [(1) and (2)]:
         Note: Approve a sufficient duration for 12 consecutive months of therapy (for example, if the patient has completed 8 months of Wegovy therapy, approve for 4 additional months).

(1) Patient has received < 12 consecutive months of Wegovy; AND
(2) According to the prescriber, the patient is continuing to titrate the Wegovy dose to a target of 1.7 mg once weekly or 2.4 mg once weekly.

2. Weight Loss, Pediatric. Approve for the duration noted if the patient meets one of the following (A or B):

A) Initial Therapy. Approve for 7 months if the patient meets the following (i, ii, iii, and iv):
- **i.** Patient is ≥ 12 years of age and < 18 years of age; AND
- **ii.** Patient has engaged in a trial of behavioral modification and dietary restriction for at least 3 months; AND
- **iii.** At baseline, patient had a BMI ≥ 95th percentile for age and sex; AND
  Note: This refers to baseline prior to any glucagon-like peptide-1 (GLP-1) agonist (e.g., Saxenda, Wegovy) or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (e.g., Zepbound).
- **iv.** Wegovy will be used concomitantly with behavioral modification and a reduced-calorie diet.

B) Patient is Continuing Therapy with Wegovy. Approve for the duration noted below if the patient meets the following (i, ii, iii, iv, and v):
Note: For a patient who has not completed 7 months of initial therapy, refer to Initial Therapy criteria above.
- **i.** Patient is ≥ 12 years of age and < 18 years of age; AND
- **ii.** At baseline, patient had a BMI ≥ 95th percentile for age and sex; AND
  Note: This refers to baseline prior to any glucagon-like peptide-1 (GLP-1) agonist (e.g., Saxenda, Wegovy) or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (e.g., Zepbound).
- **iii.** Patient has had a reduction in BMI of ≥ 1% from baseline; AND
  Note: This refers to baseline prior to any glucagon-like peptide-1 (GLP-1) agonist (e.g., Saxenda, Wegovy) or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (e.g., Zepbound).
- **iv.** Wegovy will be used concomitantly with behavioral modification and a reduced-calorie diet; AND
- **v.** Patient meets one of the following (a or b):
  i. Patient is able to tolerate a Wegovy maintenance dose of 1.7 mg once weekly or 2.4 mg once weekly: Approve for 1 year; OR
  ii. Approve for up to 5 months if the patient meets both of the following [(1) and (2)]:
  Note: Approve a sufficient duration for 12 consecutive months of therapy (for example, if the patient has completed 8 months of Wegovy therapy, approve for 4 additional months).
  i. Patient has received < 12 consecutive months of Wegovy; AND
  ii. According to the prescriber, the patient is continuing to titrate the Wegovy dose to a target of 1.7 mg once weekly or 2.4 mg once weekly.

III. Coverage of Zepbound is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Weight Loss, Adult.** Approve for the duration noted if the patient meets one of the following (A or B):
   - **A)** Initial Therapy. Approve for 8 months if the patient meets the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has engaged in a trial of behavioral modification and dietary restriction for at least 3 months; AND
     - **iii.** Patient meets one of the following (a or b):
       - **a)** At baseline, patient had a BMI ≥ 30 kg/m^2; OR
         Note: This refers to baseline prior to any glucagon-like peptide-1 (GLP-1) agonist (e.g., Saxenda, Wegovy) or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (e.g., Zepbound).
       - **b)** At baseline, patient had a BMI ≥ 27 kg/m^2 and at least one of the following weight-related comorbidities: hypertension, type 2 diabetes, dyslipidemia, obstructive sleep apnea, or cardiovascular disease; AND
         Note: This refers to baseline prior to any glucagon-like peptide-1 (GLP-1) agonist (e.g., Saxenda, Wegovy) or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (e.g., Zepbound).
     - **iv.** Zepbound will be used concomitantly with behavioral modification and a reduced-calorie diet.
   - **B)** Patient is Continuing Therapy with Zepbound. Approve for the duration noted below if the patient meets the following (i, ii, iii, iv, and v):
     Note: For a patient who has not completed 8 months of initial therapy, refer to Initial Therapy criteria above.
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient meets one of the following (a or b):
       - **a)** At baseline, patient had a BMI ≥ 30 kg/m^2; OR
         Note: This refers to baseline prior to any glucagon-like peptide-1 (GLP-1) agonist (e.g., Saxenda, Wegovy) or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (e.g., Zepbound).
       - **b)** At baseline, patient had a BMI ≥ 27 kg/m^2 and at least one of the following weight-related comorbidities: hypertension, type 2 diabetes, dyslipidemia, obstructive sleep apnea, or cardiovascular disease; AND
         Note: This refers to baseline prior to any glucagon-like peptide-1 (GLP-1) agonist (e.g., Saxenda, Wegovy) or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (e.g., Zepbound).
     - **iii.** Patient has lost ≥ 5% of baseline body weight; AND
       Note: This refers to baseline prior to any glucagon-like peptide-1 (GLP-1) agonist (e.g., Saxenda, Wegovy) or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (e.g., Zepbound).
     - **iv.** Zepbound will be used concomitantly with behavioral modification and a reduced-calorie diet; AND
     - **v.** Patient meets one of the following (a or b):
       - **a)** Patient is able to tolerate a Zepbound maintenance dose of 5 mg, 10 mg, or 15 mg once weekly: Approve for 1 year; OR
       - **b)** Approve for up to 4 months if the patient meets both of the following [(1) and (2)]:
         Note: Approve a sufficient duration for 12 consecutive months of therapy (for example, if the patient has completed 8 months of Zepbound therapy, approve for 4 additional months).

(1) Patient has received < 12 consecutive months of Zepbound; AND
(2) According to the prescriber, the patient is continuing to titrate the Zepbound dose to a target of 10 mg once weekly or 15 mg once weekly.
Note: Although 5 mg once weekly is an acceptable maintenance dose, the patient should be able to achieve the 5 mg once weekly maintenance dose within the 8 months of initial therapy provided above.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Saxenda, Wegovy, and Zepbound is not recommended in the following situations:

108. Concomitant Use with Other Weight Loss Medications. Concomitant use with other medications intended for weight loss is not recommended.[1,2,9] Note: Examples of other medications FDA-approved for weight loss include but are not limited to phentermine (Lomaira, generic), benzphetamine, diethylpropion, phendimetrazine, Contrave (naltrexone/bupropion extended-release tablets), Qsymia (phentermine/topiramate extended-release capsules), and Xenical (orlistat 120 mg capsules). Additionally, Alli (orlistat 60 mg capsules) is available over-the-counter.

109. Concomitant Use with other Glucagon-Like Peptide-1 (GLP-1) Agonists or GLP-1/ Glucose-Dependent Insulinotropic Polypeptide (GIP) Receptor Agonists. Saxenda, Wegovy, and Zepbound should not be combined with each other or with any other GLP-1 agonists.[1,2,9] Other GLP-1 and GLP-1/GIP products are FDA-approved for type 2 diabetes and are not indicated for chronic weight management. Note: Examples of other GLP-1 agonists include but are not limited to Adlyxin (lixisenatide subcutaneous [SC] injection), Byetta (exenatide SC injection), Bydureon (exenatide extended-release SC injectable suspension), Bydureon BCise (exenatide extended-release SC injectable suspension), Ozempic (semaglutide SC injection), Rybelsus (semaglutide tablets), Trulicity (dulaglutide SC injection), and Victoza (liraglutide SC injection). An example of a GLP-1/GIP agonist is Mounjaro (tirzepatide SC injection).

110. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Weight Loss – Other Appetite Suppressants and Orlistat Prior Authorization Policy

- Adipex-P® (phentermine hydrochloride capsules and tablets – Teva, generic [brand capsules obsolete 07/12/2023])
- benzphetamine 50 mg tablets (generic only)
- Contrave® (naltrexone HCl/buproprion HCl extended-release tablets – Nalpropion/Currax)
- diethylpropion hydrochloride immediate-release and controlled-release tablets (generic only)
- Lomaira™ (phentermine hydrochloride tablets – KVK-Tech)
- phendimetrazine tartrate tablets and extended-release capsules (generic only)
- phentermine hydrochloride orally disintegrating tablets (generic only)
- benzphetamine 25 mg tablets (generic only)
- Qsymia™ (phentermine and topiramate extended-release capsules – Vivus)
- Xenical® (orlistat 120 mg capsules, authorized generic – Roche, generic)

REVIEW DATE 01/03/2024

OVERVIEW

The appetite suppressant products vary slightly in the wording of their FDA-approved indications.

- **Benzphetamine**, **diethylpropion**, and **phendimetrazine** are indicated for the management of exogenous obesity as a short-term adjunct (a few weeks) to a regimen of weight reduction based on caloric restriction in patients with an initial body mass index (BMI) of ≥ 30 kg/m^2 who have not responded to a weight reducing regimen (diet and/or exercise) alone.[1-3]
- **Phentermine** hydrochloride is indicated for short-term (a few weeks) adjunctive therapy in a regimen of weight reduction based on exercise, behavioral modification, and caloric restriction in the management of exogenous obesity in those with an initial BMI ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 when other risk factors are present (e.g., controlled hypertension, diabetes mellitus, or dyslipidemia).[4-6]
- **Qsymia** is indicated as an adjunct to reduced-calorie diet and increased physical activity for chronic weight management in:[7]
    - Adults with an initial BMI of ≥ 30 kg/m^2 (obese), or ≥ 27 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes).
    - Pediatric patients ≥ 12 years of age with BMI in the 95th percentile or greater standardized for age and sex.
- **Contrave** is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of ≥ 30 kg/m^2 (obese), or ≥ 27 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes).[8]
- **Orlistat 120 mg** (Xenical, authorized generic) is indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet in patients with an initial body mass index ≥ 30 kg/m^2, or ≥ 27 kg/m^2 in the presence of at least one weight-related comorbidity (e.g., hypertension, diabetes, dyslipidemia), and to reduce the risk for weight gain after prior weight loss.[9]

Contrave

The recommended maintenance dose of Contrave is achieved at Week 4.[8] Response to therapy should be evaluated after 12 weeks at the maintenance dosage (Week 16, if dosed according to the prescribing information). If a patient has not lost ≥ 5% of baseline body weight, discontinue Contrave, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

Qsymia

The recommended starting dose of Qsymia is 3.75 mg/23 mg once daily for 14 days.[7] After 14 days, increase to 7.5 mg/46 mg once daily. Response to therapy should be evaluated by Week 12 of the 7.5 mg/46 mg dose. If an adult patient has not lost ≥ 3% of baseline body weight or pediatric patient has not lost ≥ 3% BMI, escalate the dose to 11.25 mg/69 mg once daily for 14 days, followed by an increase to 15 mg/92 mg once daily. If an adult patient has not lost ≥ 5% of baseline body weight (or a pediatric patient has not lost ≥ 5% baseline BMI) after an additional 12 weeks of treatment on Qsymia 15 mg/92 mg, discontinue Qsymia as directed as it is unlikely the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

Guidelines

Guidelines from the Endocrine Society regarding pharmacological management of obesity (2015) recommend pharmacotherapy as adjunct to behavioral modification to reduce food intake and increase physical activity for patients with BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 in the presence of at least one comorbidity, such as hypertension, dyslipidemia, type 2 diabetes, or obstructive sleep apnea.[10] If a patient's response to a weight loss medication is deemed effective (weight loss ≥ 5% of body weight at 3 months) and safe, it is recommended that the medication be continued. Although the noradrenergic weight loss medications are only labeled for short-term use, the Endocrine Society notes that off-label, long-term prescribing of phentermine is reasonable for most patients, as long as the patient has been informed that other medications for weight loss are FDA-approved for long-term use.

Per American Association of Clinical Endocrinologists/American College of Endocrinology obesity guidelines (2016), pharmacotherapy for overweight and obesity should be used only as an adjunct to lifestyle therapy and not alone.[11] The addition of pharmacotherapy produces greater weight loss and weight-loss maintenance compared with lifestyle therapy alone. The concurrent initiation of lifestyle therapy and pharmacotherapy should be considered in patients with weight-related complications that can be ameliorated by weight loss. Pharmacotherapy should be offered to patients with obesity, when potential benefits outweigh the risks, for the chronic treatment of the disease. Short-term treatment (3 to 6 months) using weight-loss medications has not been demonstrated to produce longer-term health benefits and cannot be generally recommended based on scientific evidence.

According to the American Gastroenterological Association (AGA) guideline on pharmacological interventions for adults with obesity (2022), in adults with obesity or overweight with weight-related complications who have had an inadequate response to lifestyle interventions, pharmacological agents are recommended to be added to lifestyle rather than continuing lifestyle interventions alone.[12] Wegovy® (semaglutide 2.4 mg subcutaneous injection), Saxenda® (liraglutide 3.0 mg subcutaneous injection), Qsymia, Contrave, phentermine, and diethylpropion are all listed among the suggested treatment options. Of note, although the AGA guideline suggests against the use of orlistat, it is noted that for patients who place a high value on the potential small weight loss benefit and low value on gastrointestinal adverse events, orlistat may reasonably be considered. Regarding phentermine and diethylpropion, it is noted that these are only approved as monotherapy for short-term use (12 weeks); however, given the chronic nature of weight management, many practitioners use these agents off-label for longer than 12 weeks.

Guidelines in Pediatric Obesity

Guidelines from the American Academy of Pediatrics on evaluation and treatment of children and adolescents with obesity (2023) note that pediatricians and other primary health care providers should offer adolescents ≥ 12 years of age with obesity (BMI ≥ 95th percentile) weight loss pharmacotherapy, according to medication indications, risks, and benefits, as an adjunct to health behavior and lifestyle treatment.[14]

A 2017 Endocrine Society clinical practice guideline on pediatric obesity recommends pharmacotherapy in combination with lifestyle modification be considered in obese children or adolescents only after failure of a formal program of intensive lifestyle (dietary, physical activity and behavioral) modification to limit weight gain or to ameliorate comorbidities.[13] The Endocrine Society recommends pharmacotherapy in overweight children and adolescents < 16 years only in the context of a clinical trial. Pharmacotherapy should be provided only by clinicians who are experienced in the use of anti-obesity agents and aware of the potential for adverse events. These guidelines recommend limited use of pharmacotherapy because pediatric obesity should be managed preferably as a serious lifestyle condition with important lifelong consequences.

The Endocrine Society defines overweight as BMI in at least the 85th percentile but less than the 95th percentile, and obesity as BMI in at least the 95th percentile for age and sex against routine endocrine studies, unless the height velocity is attenuated or inappropriate for the family background or stage of puberty.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of benzphetamine, diethylpropion, phendimetrazine tartrate, phentermine hydrochloride, Qsymia, Contrave, and orlistat 120 mg (Xenical, authorized generic). All approvals are provided for the durations noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Prior Authorization and prescription benefit coverage is not recommended for Alli® (orlistat 60 mg capsules).

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of benzphetamine, diethylpropion, phendimetrazine tartrate, or phentermine hydrochloride is recommended in those who meet the following:

FDA-Approved Indication

4. Weight Loss. Approve for the duration noted if the patient meets one of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets all of the following (i, ii, iii, and iv):

- Patient is ≥ 16 years of age; AND
- Patient currently has a body mass index (BMI) ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 for those with comorbidities besides obesity; AND

Note: Examples of comorbidities include diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea.

- Patient has engaged in a trial of behavioral modification and dietary restriction for at least 3 months and has failed to achieve the desired weight loss; AND
- Patient is currently engaged in behavioral modification and on a reduced calorie diet.

- Patient is Continuing Therapy. Approve for 1 year if the patient meets all of the following (i, ii, iii, and iv):

Note: For a patient who has not completed 3 months of initial therapy, criterion (1A) must be met (do not use continuation criteria if the initial 3 months were not completed).

- Patient is ≥ 16 years of age; AND
- Patient had an initial BMI ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 for those with comorbidities besides obesity: AND

Note: Examples of comorbidities include diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea.

- Patient is currently engaged in behavioral modification and on a reduced calorie diet; AND
- Patient has lost ≥ 5% of baseline body weight.

II. Coverage of Contrave is recommended in those who meet the following:

FDA-Approved Indication

1. **Weight Loss.** Approve for the duration noted if the patient meets one of the following (A or B):
   - Initial Therapy. Approve for 4 months if the patient meets the following (i, ii, iii, and iv):
     - Patient is ≥ 18 years of age; AND
     - Patient currently has a body mass index (BMI) ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 for those with comorbidities besides obesity; AND

     Note: Examples of comorbidities include diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea.

     - Patient has engaged in a trial of behavioral modification and dietary restriction for at least 3 months and has failed to achieve the desired weight loss; AND
     - Patient is currently engaged in behavioral modification and on a reduced calorie diet.
   - Patient is Continuing Therapy. Approve for 1 year if the patient meets the following (i, ii, iii, and iv):

     Note: For a patient who has not completed 4 months of initial therapy, criterion (1A) must be met (do not use continuation criteria if the initial 4 months were not completed).

     - Patient is ≥ 18 years of age; AND
     - Patient had an initial BMI ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 for those with comorbidities besides obesity: AND

     Note: Examples of comorbidities include diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea.

     - Patient is currently engaged in behavioral modification and on a reduced calorie diet; AND
     - Patient has lost ≥ 5% of baseline body weight.

III. Coverage of Qsymia is recommended in those who meet one of the following:

FDA-Approved Indications

1. **Weight Loss, Adult.** Approve for the duration noted if the patient meets one of the following (A or B):

   A) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, and iv):
   - Patient is ≥ 18 years of age; AND
   - Patient currently has a BMI ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 for those with comorbidities besides obesity; AND

   Note: Examples of comorbidities include diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea.

   - Patient has engaged in a trial of behavioral modification and dietary restriction for at least 3 months and has failed to achieve the desired weight loss; AND

- Patient is currently engaged in behavioral modification and on a reduced calorie diet.

- Patient is Continuing Therapy. Approve for 1 year if the patient meets the following (i, ii, iii, and iv):
  Note: For a patient who has not completed 6 months of initial therapy, criterion (1A) must be met (do not use continuation criteria if the initial 6 months were not completed).
  - Patient is ≥ 18 years of age; AND
  - Patient had an initial BMI ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 for those with comorbidities besides obesity; AND
    Note: Examples of comorbidities include diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea.
  - Patient is currently engaged in behavioral modification and on a reduced calorie diet; AND
  - Patient has lost ≥ 5% of baseline body weight.

2. Weight Loss, Pediatric. Approve for the duration noted if the patient meets one of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, and iv):
- **i.** Patient is ≥ 12 years of age and < 18 years of age; AND
- **ii.** Patient currently has a body mass index (BMI) of ≥ 95th percentile for age and sex; AND
- **iii.** Patient has engaged in a trial of behavioral modification and dietary restriction for at least 3 months and has failed to limit weight gain or to modify comorbidities; AND
- **iv.** Patient is currently engaged in behavioral modification and on a reduced calorie diet.

B) Patient is Continuing Therapy. Approve for 1 year if the patient meets the following (i, ii, iii, and iv):
Note: For a patient who has not completed 6 months of initial therapy, criterion (2A) must be met (do not use continuation criteria if the initial 6 months were not completed).
- **i.** Patient is ≥ 12 years of age and < 18 years of age; AND
- **ii.** Patient had an initial BMI of ≥ 95th percentile for age and sex; AND
- **iii.** Patient is currently engaged in behavioral modification and on a reduced calorie diet; AND
- **iv.** Patient has had a reduction in BMI of ≥ 5% from baseline (prior to the initiation of Qsymia).

IV. Coverage of orlistat 120 mg (Xenical, authorized generic) is recommended in those who meet one of the following:

FDA-Approved Indications

1. Weight Loss, Adult. Approve for the duration noted if the patient meets one of the following (A or B):

- Initial Therapy. Approve for 3 months if the patient meets the following (i, ii, iii, and iv):
  - Patient is ≥ 18 years of age; AND
  - Patient meets ONE of the following (a or b):
    - Patient currently has a BMI ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 for those with comorbidities besides obesity; OR

    Note: Examples of comorbidities include diabetes, dyslipidemia, hypertension, coronary heart disease, sleep apnea.
    - Patient had an initial BMI ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 for those with comorbidities besides obesity if maintaining weight loss after using a low calorie diet; AND

    Note: Examples of comorbidities include diabetes, dyslipidemia, hypertension, coronary heart disease, sleep apnea.

- Patient has engaged in a trial of behavioral modification and dietary restriction for at least 3 months and has failed to achieve the desired weight loss; AND
- Patient is currently engaged in behavioral modification and on a reduced calorie diet.

- Patient is Continuing Therapy. Approve for 1 year if the patient meets the following (i, ii, iii, and iv):

  Note: For a patient who has not completed 3 months of initial therapy, criterion (1A) must be met (do not use continuation criteria if the initial 3 months were not completed).
  - Patient is ≥ 18 years of age; AND
  - Patient had an initial BMI ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 for those with comorbidities besides obesity: AND

  Note: Examples of comorbidities include diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea.
  - Patient is currently engaged in behavioral modification and on a reduced calorie diet; AND
  - Patient has lost ≥ 5% of baseline body weight.

2. **Weight Loss, Pediatric.** Approve for the duration noted if the patient meets one of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following (i, ii, iii, and iv):
- **i.** Patient is ≥ 12 years of age and < 18 years of age; AND
- **ii.** Patient currently has a body mass index (BMI) of ≥ 95th percentile for age and sex; AND
- **iii.** Patient has engaged in a trial of behavioral modification and dietary restriction for at least 3 months and has failed to limit weight gain or to modify comorbidities; AND
- **iv.** Patient is currently engaged in behavioral modification and on a reduced calorie diet.

B) Patient is Continuing Therapy. Approve for 1 year if the patient meets the following (i, ii, iii, and iv):

Note: For a patient who has not completed 3 months of initial therapy, criterion (2A) must be met (do not use continuation criteria if the initial 3 months were not completed).
- **i.** Patient is ≥ 12 years of age and < 18 years of age; AND
- **ii.** Patient had an initial BMI of ≥ 95th percentile for age and sex; AND
- **iii.** Patient is currently engaged in behavioral modification and on a reduced calorie diet; AND
- **iv.** Patient's current BMI percentile has decreased for age and weight (taking into account that the patient is increasing in height and will have a different normative BMI from when orlistat 120 mg [Xenical, authorized generic] was started).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of benzphetamine, diethylpropion, phendimetrazine tartrate, phentermine hydrochloride, Qsymia, Contrave, and orlistat 120 mg (Xenical, authorized generic) is not recommended in the following situations:

111. **Concomitant Use with Other Weight Loss Medications.** Concomitant use with other medications intended for weight loss is not recommended. Of note, examples of medications FDA-approved for weight loss include phentermine, benzphetamine, diethylpropion, phendimetrazine, Contrave, Qsymia, orlistat 120 mg (Xenical, authorized generic), Saxenda (liraglutide subcutaneous injection), and Wegovy (semaglutide subcutaneous injection). Additionally, Alli (orlistat 60 mg capsules) is available over-the-counter.

112. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Xiaflex Prior Authorization Policy
- Xiaflex® (collagenase clostridium histolyticum intralesional injection – Endo)

REVIEW DATE: 09/06/2023

OVERVIEW

Xiaflex, a combination of bacterial collagenases, is indicated for the following uses:[1]
- **Dupuytren's contracture** with a palpable cord in adults.
- **Peyronie's disease** in adult men with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.

Disease Overview

Dupuytren's contracture is a disorder of the palmar and digital fascia of the hand.[2] Abnormal deposition of collagen initially causes nodules in the palm of the hand, which may thicken and lead to formation of cords. As the disease progresses, the cords gradually contract, leading to flexion deformities of the fingers. Joint contractures are typically painless but are associated with significant functional impairment. In clinical studies of Dupuytren's contracture, patients were eligible to participate if they had a finger contraction of 20 degrees to 100 degrees in a metacarpophalangeal joint or 20 degrees to 80 degrees in a proximal interphalangeal joint.[1]

Peyronie's disease is an acquired penile abnormality caused by fibrosis of the tunica albuginea, which may lead to pain, deformity, erectile dysfunction, and/or distress.[3] Peyronie's disease has a variable course; for most patients, pain will resolve over time without intervention, but curvature deformities are less likely to resolve without treatment. Intralesional therapy with Xiaflex may be used to treat curvature associated with Peyronie's disease and is supported by American Urological Association guidelines (2015).

Dosing Considerations

For treatment of Dupuytren's contracture, the dose of Xiaflex is 0.58 mg per injection into a palpable cord with a contracture of an metacarpophalangeal or proximal interphalangeal joint.[1] Two palpable cords affecting two joints or one palpable cord affecting two joints in the same finger may be injected per treatment visit. Injections may be administered up to three times per cord at approximately 4-week intervals.

For treatment of Peyronie's disease, one treatment course consists of four cycles.[1] Each cycle consists of two Xiaflex injection procedures (1 to 3 days apart). Up to four cycles of Xiaflex may be administered, given at approximately 6-week intervals. The safety of more than one treatment course (8 total injections) is unknown. If the curvature deformity is less than 15 degrees after the first, second, or third treatment cycle, or if further treatment is not clinically indicated, then subsequent treatment cycles should not be administered.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Xiaflex. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated

with Xiaflex, approval requires it to be administered by a healthcare provider with expertise in the condition being treated.

Prescription benefit coverage is not recommended for Xiaflex for cosmetic uses.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xiaflex is recommended in those who meet one of the following criteria:

FDA-Approved Indications

3. Dupuytren's Contracture. Approve Xiaflex for 3 months if the patient meets all of the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** At baseline (prior to initial injection of Xiaflex), the patient had contracture of a metacarpophalangeal or proximal interphalangeal joint of at least 20 degrees; AND
- **C)** As part of the current treatment course, the patient will be treated with up to three injections (maximum) per affected cord; AND
- **D)** Xiaflex is administered by a healthcare provider experienced in injection procedures of the hand and in the treatment of Dupuytren's contracture.

4. Peyronie's Disease. Approve Xiaflex for 6 months if the patient meets all of the following (A, B, C, and D):
- **A)** Patient is ≥18 years of age; AND
- **B)** Patient meets one of the following (i or ii):
  - **i.** At baseline (prior to use of Xiaflex), the patient has a penile curvature deformity of at least 30 degrees; OR
  - **ii.** In a patient who has received prior treatment with Xiaflex, the patient has a penile curvature deformity of at least 15 degrees; AND
- **C)** Patient has not previously been treated with a complete course (8 injections) of Xiaflex for Peyronie's disease; AND
- **D)** Xiaflex is being administered by a healthcare provider experienced in the treatment of male urological diseases.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xiaflex is not recommended in the following situations:

113. Cosmetic Uses (e.g., cellulite of buttocks). Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical pharmacy benefit.

114. Retreatment for Peyronie's Disease. For Peyronie's disease, the safety of more than one treatment course (8 injections) is unknown.[1]

115. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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PRIOR AUTHORIZATION POLICY

POLICY: Zokinvy Prior Authorization Policy
- Zokinvy™ (lonafarnib capsules – Eiger Biopharmaceuticals)

REVIEW DATE: 01/11/2023

OVERVIEW

Zokinvy, a protein farnesyltransferase inhibitor, is indicated in patients ≥ 12 months of age with a body surface area ≥ 0.39 m^2 for the following conditions:

- **Hutchinson-Gilford Progeria Syndrome** (HGPS), to reduce risk of mortality.
- **Progeroid laminopathies** that are processing-deficient, with either:
  - Heterozygous *LMNA* mutation with progerin-like protein accumulation; or
  - Homozygous or compound heterozygous *ZMPSTE24* mutations.[1]

Disease Overview

Hutchinson-Gilford Progeria Syndrome (HGPS)

HGPS is an ultra-rare, fatal, autosomal dominant genetic disorder with an estimated incidence of 1:4,000,000 live births and prevalence of 1:20,000,000 living individuals.[2] As of September 30, 2022, there were 18 patients identified with HGPS in the US.[3] HGPS results from a heterozygous mutation in *LMNA*, the gene encoding lamin A, a nuclear membrane protein.[4] "Classic" HGPS is caused by a single point mutation in *LMNA* involving c.1824C>T (G608G mutation) and accounts for 90% of HGPS cases.[4,5] Other *LMNA* mutations have also been identified in either the exon 11 splice junction or intron 11; these increase activation of the cryptic splice site, thus producing progerin. These are referred to as "non-classic" HGPS and comprise the remaining 10% of HGPS cases (refer to Appendix). The mutated prelamin A is referred to as progerin. Accumulation of progerin causes stiffening of the nuclear membrane and disorganized nuclear pores and chromatin, leading to hallmark symptoms including rapidly progressive atherosclerosis. Severe, rapidly progressing atherosclerosis results in an average mortality at 14.6 years of age due to myocardial infarction or stroke.[4] It is estimated that 50% of affected children have had a radiographically detectable stroke by 8 years of age.

Progeroid Laminopathies

To date, over 400 mutations in the LMNA gene have been identified, giving rise to different laminopathies which encompass a range of phenotypes including muscular dystrophy, peripheral neuropathy, lipodystrophy, and premature aging diseases.[4] Some of these may have phenotypic overlap with HGPS ("progeroid" laminopathies).[5,6] In addition, pathogenic variants in *ZMPSTE24* can result in excess prelamin A proteins and a related phenotype. As September 30, 2022, there were 13 patients identified with progeroid laminopathies in the US.[3] Of note; clinical data are not available regarding effect of Zokinvy in patients with progeroid laminopathies; the pivotal study only included patients with HGPS.

Guidelines

Formal guidelines for progeria are not in place. The Progeria Research Foundation provides a Progeria Handbook (updated March 2019) with information about the disease for patients and families, as well as for healthcare providers.[6] Clinical data with Zokinvy are acknowledged in the handbook as having positive results with regard to cardiovascular, bone, and survival outcomes. Diagnosis is made on the basis of clinical examination and genetic testing. It is noted that other progeroid laminopathies are closely related genetic diseases about which less is known. These conditions may be more or less severe than HGPS.

Applying knowledge from classic progeria (i.e., HGPS) to other progeroid syndromes may be helpful, but good judgment must be applied since patients with other progeroid syndromes will have different needs.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zokinvy. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zokinvy as well as the monitoring required for adverse events and long-term efficacy, approval requires Zokinvy to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zokinvy is recommended in those who meet the following criteria:

FDA-Approved Indication

23. Hutchinson-Gilford Progeria Syndrome. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 12 months of age; AND
- **B)** Patient has a body surface area of ≥ 0.39 m^2; AND
- **C)** Genetic testing demonstrates a confirmed pathogenic mutation in the *LMNA* gene consistent with Hutchinson-Gilford Progeria Syndrome; AND
  Note: Refer to Appendix for listing of genetic mutations associated with Hutchinson-Gilford Progeria Syndrome.
- **D)** The medication is prescribed by or in consultation with a geneticist or pediatric cardiologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zokinvy is not recommended in the following situations:

116. Progeroid Laminopathies. The efficacy of Zokinvy has not been established for patients with genetic disorders other than Hutchinson-Gilford Progeria Syndrome.[2] Although FDA labeling includes processing-deficient progeroid laminopathies, there are no clinical data demonstrating a treatment effect of Zokinvy in this population. Zokinvy is not indicated for use in processing-proficient progeroid laminopathies; based on its mechanism of action, Zokinvy would not be expected to be effective in this population.[1]

117. Other Progeroid Syndromes. Zokinvy is not indicated for use in other progeroid syndromes.[1] Based on its mechanism of action, Zokinvy would not be expected to be effective in this population.

118. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

Genetic mutations consistent with a diagnosis of Hutchinson-Gilford Progeria Syndrome are outlined below.[2,3] Of note, all of the following mutations are heterozygous; only one affected gene copy is required for confirmation of the diagnosis.

Appendix Table 1. Genetic Mutations Associated with Hutchinson-Gilford Progeria Syndrome.