CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Sickle Cell Disease – Adakveo Utilization Management Medical 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]

Adakveo is given by intravenous infusion over a period of 30 minutes at Week 0, Week 2, and every 4 weeks thereafter; the dose is 5 mg/kg.

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 medical benefit coverage of Adakveo. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 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):

i. Patient is ≥ 16 years of age; AND

ii. 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.

iii. The medication is prescribed by or in consultation with a physician who specializes in sickle cell disease (e.g., a hematologist).

Dosing. Approve the following dosing regimens (A and B):

A) Up to 5 mg/kg given by intravenous infusion at Weeks 0 and 2; AND

B) Up to 5 mg/kg given by intravenous infusion for up to once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Adakveo 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. Adakveo® intravenous infusion [prescribing information]. East Hanover, NJ: Novartis; September 2022.
2. 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.
3. 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	12/01/2021
Annual Revision	No criteria changes.	12/07/2022

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Neurology – Aduhelm Utilization Management Medical Policy
- Aduhelm™ (aducanumab-avwa intravenous infusion – Biogen/Eisai)

REVIEW DATE: 06/17/2023

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:

1. **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).

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. Aduhelm® intravenous infusion [prescribing information]. Cambridge, MA: Biogen; February 2023.
2. 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.
3. Budd Haeberlein S, Aisen PS, Barkhof F, et al. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. *J Prev Alzheimers Dis*. 2022;2(9):197-210.
4. 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.

5. Alexander GC, Emerson S, Kesselhelm AS. Evaluation of aducanumab for Alzheimer Disease scientific evidence and regulatory review involving efficacy, safety, and futility. *JAMA.* 2021;325(17):1717-1718.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	06/08/2022
Annual Revision	No criteria changes.	06/07/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Aldurazyme Utilization Management Medical 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 medical benefit coverage of Aldurazyme. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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1. **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.

   Dosing. Each dose must not exceed 0.58 mg/kg administered intravenously no more frequently than once weekly.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Aldurazyme 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. Aldurazyme® intravenous infusion [prescribing information]. Novato, CA: Genzyme; December 2019.
2. Muenzer J, Wraith JE, Clarke LA, et al. Mucopolysaccharidosis I: Management and treatment guidelines. *Pediatrics*. 2009;123:19-29.
3. Clarke LA, Atherton AM, Burton BK, et al. Mucopolysaccharidosis type I newborn screening: Best practices for diagnosis and management. *J Pediatr*. 2017;182:363-370.
4. 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.
5. Martins AM, Dualibi AP, Norato D, et al. Guidelines for the management of mucopolysaccharidosis type I. *J Pediatr*. 2009;155(Suppl 2):S32-S46.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/06/2022
Annual Revision	No criteria changes.	04/12/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Alpha$_1$-Proteinase Inhibitor Products Utilization Management Medical 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: 11/16/2022

OVERVIEW

Alpha$_1$-proteinase inhibitor (also known as alpha$_1$-antitrypsin [AAT]), is indicated for use as a chronic augmentation and maintenance therapy in adults with **alpha$_1$-proteinase deficiency** and 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]

Dosing Considerations

For AAT deficiency-associated panniculitis, limited dosing is available. A dose of 60 mg/kg once weekly is recommended in product labeling for all alpha$_1$-proteinase inhibitors for the labeled indication.[1-5]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of alpha$_1$-proteinase inhibitor. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 criteria (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.

   Dosing. Approve a dose of 60 mg/kg intravenously once weekly.

Other Uses with Supportive Evidence

2. **Alpha$_1$-Antitrypsin Deficiency-Associated Panniculitis.** Approve for 1 year if the patient is ≥ 18 years of age.

   Dosing. Approve a dose of 60 mg/kg intravenously once weekly.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of alpha$_1$-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 2022) 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 2018.
2. Zemaira® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; April 2019.
3. Prolastin®-C intravenous infusion [prescribing information]. Research Triangle Park, NC: Grifols Therapeutics; June 2018.
4. Prolastin®-C Liquid intravenous infusion [prescribing information]. Research Triangle Park, NC: Grifols Therapeutics; August 2018.
5. Glassia® intravenous infusion [prescribing information]. Lexington, MA: Shire; June 2017.
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 2020 May 21]. 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 16, 2022.

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 2022. Available at: https://goldcopd.org/2022-gold-reports-2/. Accessed on November 14, 2022.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Conditions Not Recommended for Approval:** "Cystic Fibrosis" was removed from Conditions Not Recommended for Approval.	11/17/2021
Annual Revision	**Alpha$_1$-Antitrypsin Deficiency with Emphysema (or Chronic Obstructive Pulmonary Disease):** The requirement regarding baseline (pretreatment) serum alpha$_1$-antitrypsin concentration was clarified to note that a value of < 11 mcM corresponds with a value of < 80 mg/dL if measured by radial immunodiffusion or < 57 mg/dL if measured by nephelometry. Previously, the different cutoff values for varying assay methods were not specified.	11/16/2022

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hemophilia – Altuviiio Utilization Management Medical 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.

Dosing Considerations

Dosing of clotting factor concentrates is highly individualized. The National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC) provides recommendations regarding doses of clotting factor concentrate in the home (2016).[8] The number of required doses varies greatly and is dependent on the severity of the disorder and the prescribed regimen. Per MASAC guidance, patients on prophylaxis should also have a minimum of one major dose and two minor doses on hand for breakthrough bleeding in addition to the prophylactic doses used monthly. The guidance also notes that an adequate supply of clotting factor concentrate is needed to accommodate weekends and holidays. Therefore, maximum doses in this policy allow for prophylactic dosing plus three days of acute bleeding or perioperative management per 28 days. Doses exceeding this quantity will be reviewed on a case-by-case basis by a clinician.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage Altuviiio. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the criteria and dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 for patients who meet the following criteria:

FDA-Approved Indication

1. 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; OR

B) Patient is 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.

Dosing. Approve the following dosing regimens (A, B, and/or C):

A) Routine prophylaxis: approve up to 50 IU/kg intravenously no more frequently than once weekly; AND/OR
B) On demand treatment and control of bleeding episodes: approve up to 50 IU per kg intravenously with additional doses once every 2 to 3 days for up to 10 days per episode; AND/OR
C) Perioperative management of bleeding: approve up to 50 IU per kg intravenously and provide for additional doses once every 2 to 3 days for up to 10 days per procedure.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Altuviiio 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. Altuviiio™ intravenous injection [prescribing information]. Waltham, MA: Bioverativ/Sanofi; February 2023.
2. 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.
3. Croteau SE. Hemophilia A/B. *Hematol Oncol Clin North Am*. 2022;36(4):797-812.
4. Franchini M, Mannucci PM. The more recent history of hemophilia treatment. *Semin Thromb Hemost*. 2022;48(8):904-910.
5. Peyvandi F, Garagiola I, Young G. The past and future of haemophilia: diagnosis, treatments and its complications. *Lancet*. 2016;388(10040):187-197.
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. Available at: https://www.hemophilia.org/sites/default/files/document/files/272_Treatment.pdf. Accessed on March 20, 2023.
7. Srivastava A, Santagostino E, Dougall A, et al, on behalf of the WFH guidelines for the management of hemophilia panelists and coauthors. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia*. 2020;26(Suppl 6):1-158.
8. National Hemophilia Foundation. MASAC (Medical and Scientific Advisory Council) recommendations regarding doses of clotting factor concentrate in the home (Revised June 7, 2016). MASAC Document #242. Adopted on September 3, 2020. Available at: https://www.hemophilia.org/sites/default/files/document/files/242.pdf. Accessed on March 20, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	03/29/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Muscular Dystrophy – Amondys 45 Utilization Management Medical 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.

REFERENCES

1. Amondys 45 intravenous infusion [prescribing information]. Cambridge, MA: Sarepta; February 2021.
2. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *Lancet Neurol*. 2018;17(3):251-267.
3. Shimizu-Motohashi Y, Murakami T, Kimura E, et al. Exon skipping for Duchenne muscular dystrophy: a systematic review and meta-analysis. *Orphanet J Rare Dis*. 2018;13(1):93.
4. US National Institutes of Health. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2023 Feb 10]. Available from: https://clinicaltrials.gov/ct2/show/NCT02500381. Search term: NCT02500381.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	02/16/2022
Update	08/12/2022: A summary of the shortcomings of clinical data with Amondys 45 were added to the denial rationale.	NA
Annual Revision	No criteria changes.	02/15/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Amyloidosis – Amvuttra Management Medical Policy
- Amvuttra™ (vutrisiran subcutaneous injection – Alnyam)

REVIEW DATE: 06/28/2023

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 injection) 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 medical benefit coverage of Amvuttra. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 history 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.

   Dosing. Approve the following dosing regimen (A and B):
   - **A)** The dose is 25 mg by subcutaneous injection; AND
   - **B)** The dose is administered not more frequently than once every 3 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Amvuttra is not recommended in the following situations:

1. **Concomitant Use With Onpattro (patisiran intravenous injection), 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 and Tegsedi 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]

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. Amvuttra™ subcutaneous injection [prescribing information]. Cambridge, MA: Alnylams; February 2023.
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.
3. 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.
4. 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.
5. 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.
6. Adams D, Tournev IL, Talor MS, et al. Efficacy and safety of vutrisitan for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid.* 2023; 30(1):1-9.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	06/29/2022
Annual Revision	No criteria changes.	06/28/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Amyloidosis – Onpattro Utilization Management Medical Policy
- Onpattro® (patisiran intravenous infusion – Alnylam)

REVIEW DATE: 11/30/2022

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.

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 were noted.

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] 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 medical benefit coverage of Onpattro. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e.,

Medical Director or Pharmacist). 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):
   - **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)** The medication is prescribed by or in consultation with a neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis.

   Dosing. Approve the following dosing (A and B):
   - **A)** The dose is up to 0.3 mg/kg given intravenously up to a maximum dose of 30 mg; AND
   - **B)** The dose is administered not more frequently than once every 3 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Onpattro is not recommended in the following situations:

1. **Concomitant Use With Amvuttra (vutrisiran subcutaneous injection), Tegsedi, 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, and Tegsedi 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.[7] 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.[8]

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. Onpattro® [prescribing information]. Cambridge, MA: Alnylam; July 2022.
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.
3. 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.
4. 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.
5. 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.
6. Schmidt HH, Wixner J, Plante-Bordeneuve V; on behalf of the Patisiran Post-LT Study Group. Patisiran treatment in patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy after liver transplantation. *Am J Transplant.* 2022;22:1646-1657.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/17/2021
Selected Revision	**Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis (hATTR):** Criteria requiring the patient to have tried or is currently receiving at least one systemic agent for symptoms of polyneuropathy from one of the following pharmacologic classes: a gabapentin-type product, duloxetine, or a tricyclic antidepressant was removed. **Concomitant Use With Amvuttra (vutrisiran subcutaneous injection), Tegsedi (inotersen subcutaneous injection), or a Tafamidis Product:** Amvuttra was added to this condition not recommended for approval.	06/29/2022
Annual Revision	**Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis (hATTR):** The criterion requiring the patient did not have a history of liver transplantation was removed.	11/30/2022

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Amyloidosis – Tegsedi Utilization Management Medical Policy
- Tegsedi® (inotersen subcutaneous injection – Ionis/Akcea Therapeutics)

REVIEW DATE: 11/16/2022

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 atment 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 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 ATTR.[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 medical benefit coverage of Tegsedi. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the criteria and dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 history 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.

   Dosing. Approve 284 mg subcutaneously once weekly.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tegsedi is not recommended in the following situations:

1. **Concomitant Use With Amvuttra (vutrisiran subcutaneous injection), Onpattro (patisiran lipid complex intravenous infusion), 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 Onpattro and Tegsedi did not allow concurrent use of tetramer stabilizers (e.g., tafamidis, diflunisal). A scientific statement from the American Heart Association notes that there is little data to support combination therapy for these products.[3]

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. Tegsedi® injection [prescribing information]. Waltham, MA: Sobi/Akcea; June 2022.
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.
3. 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.
4. 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/17/2021
Selected Revision	**Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis (hATTR):** Criteria requiring the patient to have tried or is currently receiving at least one systemic agent for symptoms of polyneuropathy from one of the following pharmacologic classes: a gabapentin-type product, duloxetine, or a tricyclic antidepressant was removed. **Concomitant Use With Amvuttra (vutrisiran subcutaneous injection), Onpattro (patisiran lipid complex intravenous infusion), or a Tafamidis Product.** Amvuttra was added to this condition not recommended for coverage.	06/29/2022
Annual Revision	No criteria changes.	11/16/2022

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Human Immunodeficiency Virus – Apretude Utilization Management Medical 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]

Oral Lead-in (at Least 28 Days)	IM (Gluteal) Initiation Injection (Month 2 and Month 3)	IM (Gluteal) Continuation Injection (Month 5 and Q2M Onwards)
Vocabria 30 mg QD for 28 days	Apretude 600 mg (3 mL)[a]	Apretude 600 mg (3 mL)[b]

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]

IM (Gluteal) Initiation Injection (Month 1 and Month 2)	IM (Gluteal) Continuation Injection (Month 4 and Q2M Onwards)
Apretude 600 mg (3 mL)[a]	Apretude 600 mg (3 mL)[a]

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]

Time Since Last Injection	Recommendation
Initiation Injection – If the second injection is missed and time since first injection is:	
≤ 2 months	Administer Apretude (600 mg) as soon as possible, then continue to follow the Q2M injection dosing schedule.
> 2 months	Restart Apretude (600 mg) with one injection, followed by a second injection (600 mg) 1 month later. Then continue to follow the Q2M injection dosing schedule thereafter (starting at Month 4).
Maintenance Injection – If third or subsequent injection is missed and time since prior injection is:	
≤ 3 months	Administer Apretude as soon as possible, then continue with the Q2M injection dosing schedule.
> 3 months	Restart Apretude (600 mg) with one injection, followed by a second injection (600 mg) 1 month later. Then continue to follow the Q2M injection dosing schedule thereafter (starting at Month 4).

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.[2] 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]

	Recommendation for PrEP	Evidence Rating
Apretude[a]	For adults and adolescents who report sexual behaviors that place them at substantial ongoing risk of HIV exposure and acquisition.	IA
FTC/TDF	For adult and adolescent (≥ 35 kg) **men and women**: • **Sexually active individuals** who report sexual behaviors that place them at substantial ongoing risk of HIV exposure and acquisition; OR • **IDU** and report injection practices that place them at substantial ongoing risk of HIV exposure and acquisition.	1A

Table 4 (continued). US Public Health Service PrEP Recommendations (December 2021).[2]

	Recommendation for PrEP	Evidence Rating
Descovy	For adult and adolescent (≥ 35 kg) **cis-gender men**[*] and **transgender women**[†]**:** • **Sexually active individuals** who report sexual behaviors that place them at substantial ongoing risk of HIV exposure and acquisition. Descovy PrEP has **not been studied in cis-gender women**[‡] and is **not recommended** for HIV prevention for women or other individuals at risk through receptive vaginal sex (IA).	IA (cis-gender men) IIB (transgender women)

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 history 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 medical benefit coverage of Apretude. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **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.

   Dosing. Approve the following dosing regimens (A or B):
   - **A)** Approve 600 mg intramuscularly for one dose, followed by 600 mg for a second dose 1 month later, then approve 600 mg intramuscularly once every 2 months thereafter.
   - **B)** If Apretude will be given concomitantly with rifabutin, approve Apretude 600 mg intramuscularly for one dose, followed by 600 mg for a second dose 2 weeks later, then approve 600 mg intramuscularly once-monthly thereafter.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Apretude is not recommended in the following situations:

1. **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]

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. Apretude® injectable suspension [prescribing information]. Research Triangle Park, NC: ViiV; December 2021.
2. Centers for Disease Control and Prevention: US Public Health Service: Preexposure prophylaxis for the prevention of HIV infection in the United States—2021 Update: a clinical practice guideline. Available at: https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf. Published December 2021. Accessed on: January 25, 2023.
3. Ghandi RT, Bedimo R, and Hoy JF, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults. 2022 recommendations of the International Antiretroviral Society-USA Panel. *JAMA*. 2023;329(1):63-84.
4. Guidelines on long-acting injectable cabotegravir for HIV prevention. Geneva: World Health Organization; 2022. License: CC BY-NC-SA 3.0 IGO. Available at: https://www.who.int/publications/i/item/9789240054097. Accessed on January 25, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/26/2022
Annual Revision	No criteria changes.	01/25/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Bone Modifiers – Evenity Utilization Management Medical 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 history 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 medical benefit coverage of Evenity. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Coverage is limited to 12 monthly doses during the therapy course. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indication

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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) The 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 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; 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.

Dosing. Approve 210 mg of Evenity subcutaneously once every month for no more than 12 monthly doses during a therapy course.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Evenity is not recommended in the following situations:

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

2. **Concurrent Use of 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.

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

1. Evenity® subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; April 2020.
2. Shoback D, Rosen CJ, Black DM, et al. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society guideline update. *J Clin Endocrinol Metab*. 2020;105(3):587-594.
3. LeBoff MS, Greenspan SL, Insogna KL, et al. The clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int*. 2022;33:2049-2102.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Conditions Not Recommended for Approval:** To the Note which lists the medications that should not be used with Evenity, it was clarified that this does NOT exclude use of calcium and/or vitamin D supplements in combination with Evenity.	05/18/2022
Annual Revision	**Osteoporosis – Treatment for a Postmenopausal Patient:** The exception that the patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy was removed. Instead, this exception was incorporated into a Note that lists osteoporotic fracture or a fragility fracture as an example of inadequate efficacy or significant intolerance to a trial of an oral bisphosphonate or an oral bisphosphonate-containing product.	05/24/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Bone Modifiers – Ibandronate Intravenous Utilization Management Medical 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 medical benefit coverage of ibandronate injection. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. 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 must meet 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.

Dosing. Approve 3 mg intravenously no more frequently than once every 3 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

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

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

2. **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, generic), 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.

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

1. Boniva® intravenous infusion [prescribing information]. South San Francisco, CA: Genentech/Roche; January 2022.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	03/09/2022
Annual Revision	The brand name of Boniva was removed from the title of the policy. **Osteoporosis – Treatment of a Postmenopausal Patient:** The requirement that the patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy was removed. Instead, this requirement was incorporated into a Note that lists osteoporotic fracture or a fragility fracture as an example of inadequate efficacy or significant intolerance to a trial of an oral bisphosphonate or an oral bisphosphonate-containing product. **Concurrent Use of Ibandronate Injection with Other Medications for Osteoporosis:** To the Note which lists the medications that should not be used with ibandronate injection, it was clarified that this does NOT exclude use of calcium and/or vitamin D supplements in combination with ibandronate injection.	03/22/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Bone Modifiers – Zoledronic Acid (Reclast) Utilization Management Medical 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 medical benefit coverage of zoledronate acid (Reclast). Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 zoledronate acid (Reclast) is recommended in those who meet one of 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.

Dosing. Approve one 5 mg infusion given intravenously (IV) up to once every year.

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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.

Dosing. Approve one 5 mg infusion given intravenously (IV) up to once every 2 years.

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3. Osteoporosis – Treatment for a Man*. Approve for 1 year if the patient meets the following criteria (A and B):

A) The 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: 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)** The 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.

Dosing. Approve one 5 mg infusion given intravenously up to once every year.

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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, b, or c):
  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.

Dosing. Approve one 5 mg infusion given intravenously up to once every year.

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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, or 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.

Dosing. Approve one 5 mg intravenous (IV) infusion.

Other Uses with Supportive Evidence

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6. Osteogenesis Imperfecta. Approve for 1 year.

Dosing. Dosing information is limited. Approve up to 0.05 mg per kg intravenous (IV) given no more frequently than once every 3 months.

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 (alendronate, risedronate, ibandronate), other intravenous bisphosphonates (e.g., intravenous ibandronate [Boniva]), Evenity (romosozumab-aqqg subcutaneous injection), Prolia (denosumab subcutaneous injection), Forteo (teriparatide subcutaneous injection, generic), Tymlos (abaloparatide subcutaneous injection), and calcitonin nasal spray. This applies only to 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.

REFERENCES

1. Reclast® intravenous infusion [prescribing information]. East Hanover, NJ: Novartis; April 2020.
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5. Panigrahi I, Das RR, Sharda S, et al. Response to zoledronic acid in children with type III osteogenesis imperfecta. *J Bone Miner Metab*. 2010;28:451-455.
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8. Dwan K, Phillipi CA, Steiner RD, Basel D. Bisphosphonate therapy for osteogenesis imperfecta. *Cochrane Database Syst Rev*. 2016;10:CD005088.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	03/09/2022
Annual Revision	**Glucocorticoid-Induced Osteoporosis – Prevention and Treatment:** The exception that the patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy was removed. Instead, this exception was incorporated into a Note that lists osteoporotic fracture or a fragility fracture as an example of inadequate efficacy or significant intolerance to a trial of an oral bisphosphonate or an oral bisphosphonate-containing product. **Osteoporosis – Prevention for a Postmenopausal Patient:** The exception that the patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy was removed. Instead, this exception was incorporated into a Note that lists osteoporotic fracture or a fragility fracture as an example of inadequate efficacy or significant intolerance to a trial of an oral bisphosphonate or an oral bisphosphonate-containing product. **Osteoporosis – Treatment for a Man:** The exception that the patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy was removed. Instead, this exception was incorporated into a Note that lists osteoporotic fracture or a fragility fracture as an example of inadequate efficacy or significant intolerance to a trial of an oral bisphosphonate or an oral bisphosphonate-containing product. **Osteoporosis – Treatment for a Postmenopausal Patient:** The exception that the patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy was removed. Instead, this exception was incorporated into a Note that lists osteoporotic fracture or a fragility fracture as an example of inadequate efficacy or significant intolerance to a trial of an oral bisphosphonate or an oral bisphosphonate-containing product. **Conditions Not Recommended for Approval:** Regarding **Concurrent Use of Zoledronic Acid Injection (Reclast) with Other Medications for Osteoporosis**, to the Note which lists the medications that should not be used with zoledronic acid injection (Reclast), it was clarified that this does NOT exclude use of calcium and/or vitamin D supplements in combination with zoledronic acid injection (Reclast).	03/22/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Botulinum Toxins – Botox Utilization Management Medical 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.[39,40] 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).[41,42]

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; history 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]

Dosing Considerations

Definitive dosing has not been established for off-label uses of botulinum toxins, including Botox. In general, Botox is not recommended to be injected more frequently than once every 3 months, and botulinum toxins appear to have an approximately 3-month duration of effect or longer, depending on the site of injection. The Botox prescribing information advises that in a 3-month interval, adults should not exceed a total dose of 400 units. Pediatric patients should not exceed a total dose of the lesser of 10 units/kg or 340 units in a 3-month interval. Specific considerations by indication are noted below:

- **Achalasia:** Botox has been studied for achalasia in several trials. Doses higher than 100 units per treatment have not been shown to be more effective.[34]
- **Sialorrhea, Chronic:** Xeomin® (incobotulinumtoxinA injection) is indicated for this use.[35] Per Xeomin labeling, the maximum recommended dose for adults is 100 units (50 units per side) and for pediatric patients is 75 units (37.5 units per side), administered not more frequently than once every 16 weeks. Recommendations for maximum dosing and frequency for Botox are based on suggested relative conversion of 1:1 for Botox to Xeomin.[36,37]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Botox. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Requests for doses outside the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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]**.

Medical 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.

   Dosing. Approve up to a maximum dose of 200 units, administered not more frequently than once every 3 months.

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.

   Dosing. Approve up to a maximum dose of 300 units, administered not more frequently than once every 3 months.

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).

   Dosing. Approve up to a maximum dose of 50 units per axilla, administered not more frequently than once every 3 months.

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.

Dosing. Approve up to a maximum dose of 155 units, administered not more frequently than once every 12 weeks.

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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.

Dosing. Approve up to a maximum dose of 200 units, administered not more frequently than once every 12 weeks.

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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.

Dosing. Approve up to a maximum dose of 100 units, administered not more frequently than once every 12 weeks.

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7. Spasticity, Limb. Approve for 1 year if the patient is ≥ 2 years of age.

Dosing. Approve one of the following regimens (A or B):

A) Lower limb spasticity: Approve one of the following regimens (i or ii):

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i. Patient is ≥ 18 years of age: Approve up to a maximum dose of 400 units, administered not more frequently than once every 12 weeks.
ii. Patient is < 18 years of age: Approve up to a maximum dose of 8 units/kg (not to exceed 300 units), administered not more frequently than once every 12 weeks.

B) Upper limb spasticity: Approve one of the following regimens (i or ii):
i. Patient is ≥ 18 years of age: Approve up to a maximum dose of 400 units, administered not more frequently than once every 12 weeks.
ii. Patient is < 18 years of age: Approve up to a maximum dose of 6 units/kg (not to exceed 200 units), administered not more frequently than once every 12 weeks.

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8. Strabismus. Approve for 1 year if the patient is ≥ 12 years of age.

Dosing. Approve up to a maximum dose of 25 units in any one muscle, administered not more frequently than once every 3 months.

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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, or 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.

Dosing. Approve up to a maximum dose of 200 units, administered not more frequently than once every 12 weeks.

Other Uses with Supportive Evidence

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10. Achalasia. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 100 units, administered not more frequently than once every 3 months.

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11. Anal Fissure. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

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12. Chronic Facial Pain/Pain Associated with Temporomandibular Dysfunction. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

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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 the 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.

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

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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.

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

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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, topiramate.

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

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16. Hemifacial Spasm. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

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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.

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

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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).

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

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19. Myofascial Pain. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

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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.

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

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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, or stretching.

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

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22. Sialorrhea, Chronic. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 100 units (50 units per side), administered not more frequently than once every 16 weeks.

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 medical 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).[38] 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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HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Hemifacial Spasm:** This Other Use with Supportive Evidence was reworded to as listed; previously, the indication was titled "Spasticity, other than Limb (i.e., spasticity or hypertonia due to cerebral palsy, stroke, brain injury, spinal cord injury, multiple sclerosis, hemifacial spasm)".	01/11/2023
Selected Revision	**Migraine Headache Prevention:** The following sentence was added to the current Note regarding the requirement for standard prophylactic (preventative) pharmacologic therapies**:** 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]. The Overview was updated to include a list of medications with established efficacy from the American Headache Society for the treatment of migraine prevention.	08/02/2023
Update	08/08/2023: The Overview was updated to include the following sentence: Additionally, the following treatments are possibly effective and can be considered for migraine prevention: calcium channel blocker (e.g., verapamil) and angiotensin converting enzyme inhibitors (e.g., lisinopril).	N/A
Early Annual Revision	**Blepharospasm**: Diagnosis was changed from "Blepharospasm associated with dystonia or Strabismus" to "Blepharospasm" with the following Note added: "This includes blepharospasm associated with dystonia, including benign essential blepharospasm and	10/11/2023

	seventh (VII) nerve disorders." An age requirement of ≥ 12 years was added. Previously there was not an age requirement in place. **Cervical Dystonia**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. **Hyperhidrosis, Primary Axillary**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. **Migraine Headache Prevention**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. **Neurogenic Detrusor Overactivity (NDO), Pediatric:** New indication, age ≥ 5 years, criteria, and dosing added. Previously, diagnosis and dosing was captured under FDA Labeled Indications as "Urinary Incontinence Associated with a Neurological Condition". **Overactive Bladder with Symptoms of Urge Urinary Incontinence, Urgency, and Frequency (Adult)**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. "Adult" was added to diagnosis to distinguish from pediatric NDO indication. **Spasticity, Limb**: An age requirement of ≥ 2 years was added. Previously there was not an age requirement in place. **Strabismus**: New indication, requirement of age ≥ 12 years, criteria, and dosing added. Previously, diagnosis and dosing was captured under FDA Labeled Indications as "Blepharospasm associated with dystonia or Strabismus". **Urinary Incontinence Associated with a Neurological Condition (Adult)**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. "Adult" was added to diagnosis to distinguish from pediatric NDO indication. Dosing considerations for patients ≤ 18 years of age were removed. **Achalasia**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Anal Fissure**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Chronic Facial Pain/Pain Associated with Temporomandibular Dysfunction**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Chronic Low Back Pain**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Dystonia other than cervical**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Essential Tremor**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Hemifacial Spasm**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Hyperhidrosis, Gustatory**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Hyperhidrosis, Palmar/Plantar and Facial**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Myofascial Pain**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Ophthalmic Disorders, other than Blepharospasm or Strabismus**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Plantar Fasciitis**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed.	

	Sialorrhea, Chronic: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed.	

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Botulinum Toxin – Daxxify Utilization Management Medical 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.

Dosing Considerations

After reconstitution, the recommended dose of Daxxify for the treatment of cervical dystonia ranges from 125 units to 250 units given intramuscularly as a divided dose among affected muscles.[1] In patients previously treated with another botulinum toxin, their past dose, response to treatment, duration of effect, and adverse event history should be taken into consideration when determining the Daxxify dose. If dose modification is necessary, dose adjustments can be made in 50 to75 unit increments according to individual patient response. Daxxify should be administered no more frequently than once every 3 months for any indication.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Daxxify. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Requests for doses outside the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for 1 year in duration.

Medical benefit coverage is 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.

Dosing. Approve up to a maximum dose of 300 units, administered not more frequently than once every 3 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Daxxify 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, 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 medical 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

1. Daxxify® injection [prescribing information]. Newark, CA: Revance; August 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/30/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Botulinum Toxin – Dysport Utilization Management Medical 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]

Dosing Considerations

Toxin distribution varies between the commercially available botulinum toxin products.[1,14,15] The labels for the botulinum toxin products state that there is a lack of interchangeability between the products for various reasons, including differences in the units of biological activity. Studies have attempted to establish a conversion ratio between botulinum toxin products, with variable results.[18] In general, conversion ratios of 1:1 for Botox to Xeomin, 1:3 for Botox to Dysport, and 1:50 to 1:100 for Botox to Myobloc have been suggested.

Definitive dosing has not been established for off-label uses of botulinum toxins, including Dysport. Specific dosing considerations by indication are noted below. For other indications addressed in this policy,

specific dosing guidance is not available. In these cases, dosing is based on the Botox prescribing information, which states that in a 3-month interval, adults should not exceed a total dose of 400 units, and pediatric patients should not exceed a total dose of the lesser of 10 units/kg or 340 units in a 3-month interval.[14] Recommendations for maximum dosing and frequency for Dysport are based on a suggested relative conversion of 3:1 between Dysport and Botox units.[1] Additionally, the maximum dose supported for a patient < 18 years of age in Dysport labeling is 30 units/kg (not to exceed 1,000 units). Specific considerations by indication are noted below.

- **Blepharospasm:** A maximum dose of 120 units of Dysport, not more frequently than once every 12 weeks, has been suggested.[16,17]
- **Sialorrhea, Chronic:** Xeomin is indicated for this use.[15] Per Xeomin labeling, the maximum recommended dose for adults is 100 units (50 units per side) and for pediatric patients is 75 units (37.5 units per side), administered not more frequently than once every 16 weeks.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Dysport. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Requests for doses outside the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for 1 year in duration.

Medical 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

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1. 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.

Dosing. Approve up to a maximum dose of 1,000 units, administered not more frequently than once every 12 weeks.

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2. Spasticity, Limb. Approve for 1 year if the patient is ≥ 2 years of age.

Dosing. Approve one of the following regimens (A or B):

A) Lower limb spasticity (or combined upper and lower limb spasticity): Approve one of the following regimens (i or ii):
  - **i.** Patient is ≥ 18 years of age: Approve up to a maximum dose of 1,500 units, administered not more frequently than once every 12 weeks.
  - **ii.** Patient is < 18 years of age: Approve up to a maximum dose of 30 units/kg (not to exceed 1,000 units), administered not more frequently than once every 12 weeks.

B) Upper limb spasticity: Approve one of the following regimens (i or ii):
  - **i.** Patient is ≥ 18 years of age: Approve up to a maximum dose of 1,000 units, administered not more frequently than once every 12 weeks.

ii. Patient is < 18 years of age: Approve up to a maximum dose of 16 units/kg (not to exceed 640 units), administered not more frequently than once every 12 weeks.

Other Uses with Supportive Evidence

3. Anal Fissure. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 1,200 units, administered not more frequently than once every 3 months.

4. 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.

Dosing. Approve up to a maximum dose of 120 units, administered not more frequently than once every 12 weeks.

5. Hemifacial Spasm. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 1,200 units, administered not more frequently than once every 3 months.

6. Sialorrhea, Chronic. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 300 units (150 units per side), administered not more frequently than once every 16 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Dysport 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 medical 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. 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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HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Hemifacial Spasm:** This Other Use with Supportive Evidence was reworded to as listed; previously, the indication was titled "Spasticity, other than Limb (i.e., spasticity or hypertonia due to cerebral palsy, stroke, brain injury, spinal cord injury, multiple sclerosis, hemifacial spasm)". **Hyperhidrosis, Gustatory:** This Other Use with Supportive Evidence was removed from the policy. **Hyperhidrosis, Primary Axillary:** This Other Use with Supportive Evidence was removed from the policy.	01/11/2023
Early Annual Revision	**Cervical Dystonia**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. **Spasticity, Limb**: An age requirement of ≥ 2 years was added. Previously there was not an age requirement in place. **Anal Fissure**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Blepharospasm**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. The following note was added to the indication: "This includes blepharospasm associated with dystonia, benign essential blepharospasm, seventh (VII) nerve disorders." **Hemifacial Spasm**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed. **Sialorrhea, Chronic**: An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. Dosing considerations for patients ≤ 18 years of age were removed.	10/11/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Botulinum Toxins – Myobloc Utilization Management Medical 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).

Dosing Considerations

Definitive dosing has not been established for off-label uses of botulinum toxins, including Myobloc. Recommendations for maximum dosing and frequency for Myobloc are based on a suggested relative conversion of 50:1 between Myobloc and Botox units.[3] For **Spasticity, Upper Limb**, dosing is based on the Botox prescribing information, which states that in a 3-month interval, adults should not exceed a total dose of 400 units.[4]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Myobloc. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Requests for doses outside the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the dosing interval is provided in months, 1 month is equal to 30 days.

Medical benefit coverage is 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.

Dosing. Approve up to a maximum dose of 5,000 units, administered not more frequently than once every 12 weeks.

2. Sialorrhea, Chronic. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 3,500 units (1,750 units per side), administered not more frequently than once every 12 weeks.

Other Uses with Supportive Evidence

3. Spasticity, Upper Limb. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve up to a maximum dose of 20,000 units, administered not more frequently than once every 3 months.

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 medical 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

1. Myobloc® injection [prescribing information]. San Francisco, CA: Solstice Neurosciences; September 2020.
2. Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache. Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2016;86:1818-1826.
3. Walker TJ, Dayan SH. Comparison and overview of currently available neurotoxins. *Clin Aesthet Dermatol*. 2014;7(21):31-39.
4. Botox® injection [prescribing information]. Madison, NJ: Allergan; August 2022.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Bladder Dysfunction:** This Other Use with Supportive Evidence was removed from the policy. **Myofascial Pain:** This Other Use with Supportive Evidence was removed from the policy.	07/13/2022
Early Annual Revision	**Cervical Dystonia:** An age requirement of ≥ 18 years was added to criteria. Previously there was not an age requirement in place. **Sialorrhea, Chronic:** An age requirement of ≥ 18 years was added to criteria. Previously there was not an age requirement in place. **Hyperhidrosis, Palmar or Primary Axillary:** This Other Use with Supportive Evidence was removed from the policy. **Spasticity, Upper Limb:** This Other Use with Supportive Evidence was reworded as listed; previously the indication was listed as "Spasticity (i.e., spasticity due to cerebral palsy, stroke, brain injury, spinal cord injury, multiple sclerosis, hemifacial spasm)". Additionally, an age requirement of ≥ 18 years was added to criteria. Previously there was not an age requirement in place. With this change, pediatric dosing was removed from the dosing section.	01/11/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Botulinum Toxin – Xeomin Utilization Management Medical 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 medical benefit coverage of Xeomin. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below.

Medical 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

1. 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.

Dosing. Approve up to a maximum dose of 100 units (50 units per eye), administered not more frequently than once every 12 weeks.

2. 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.

Dosing. Approve up to a maximum dose of 120 units, administered not more frequently than once every 12 weeks.

3. Sialorrhea, Chronic. Approve for 1 year if the patient is ≥ 2 years of age.

Dosing. Approve one of the following regimens (A or B):
A) Patient is ≥ 18 years of age: Approve up to a maximum dose of 100 units (50 units per side), administered not more frequently than once every 16 weeks.
B) Patient is < 18 years of age: Approve up to a maximum dose of 75 units (37.5 units per side), administered not more frequently than once every 16 weeks.

4. Spasticity, Upper Limb. Approve for 1 year if the patient is ≥ 2 years of age.

Dosing. Approve one of the following regimens (A or B):
A) Patient is ≥ 18 years of age: Approve up to a maximum dose of 400 units, administered not more frequently than once every 12 weeks.
B) Patient is < 18 years of age: Approve up to a maximum dose of 16 units/kg (not to exceed 400 units), administered not more frequently than once every 12 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xeomin 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 medical 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. 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. Xeomin® injection [prescribing information]. Raleigh, NC and Franksville, WI: Merz; August 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Hyperhidrosis, Primary Axillary, Palmar/Plantar, and Facial:** This Other Use with Supportive Evidence was removed from the policy. **Spasticity, other than Upper Limb:** This Other Use with Supportive Evidence was removed from the policy.	01/11/2023
Early Annual Revision	**Blepharospasm:** An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. The following note was added to the indication: "This includes blepharospasm associated with dystonia, benign essential blepharospasm, seventh (VII) nerve disorders." **Cervical Dystonia:** An age requirement of ≥ 18 years was added. Previously there was not an age requirement in place. **Sialorrhea, Chronic:** An age requirement of ≥ 2 years was added. Previously there was not an age requirement in place. **Spasticity, Upper Limb**: An age requirement of ≥ 2 years was added. Previously there was not an age requirement in place.	10/11/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Complement Inhibitors – Soliris Utilization Management Medical Policy
- Soliris® (eculizumab intravenous infusion – Alexion)

REVIEW DATE: 09/20/2023

OVERVIEW

Soliris, a complement 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 medical benefit coverage of Soliris. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing

documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the dosing interval is provided 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

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1. Atypical Hemolytic Uremic Syndrome. Approve for 1 year if the patient meets the following (A and B):
- **A)** Patient does not have Shiga toxin *Escherichia coli*-related hemolytic uremic syndrome; AND
- **B)** The medication is being prescribed by or in consultation with a nephrologist.

Dosing. Approve if the dose meets ONE of the following (A or B):
- **A)** For patients ≥ 18 years of age, the dose is administered intravenously and meets ONE of the following (i or ii):
  - **i.** The dose is ≤ 900 mg weekly for the first 4 weeks; OR
  - **ii.** The dose is ≤ 1,200 mg every 2 weeks thereafter.
- **B)** For patients < 18 years of age, the dose is administered intravenously and meets ONE of the following (i, ii, iii, iv, or v):
  - **i.** ≥ 40 kg: 900 mg weekly x 4 doses, 1,200 mg at week 5; then 1,200 mg every 2 weeks; OR
  - **ii.** 30 kg to < 40 kg: 600 mg weekly x 2 doses, 900 mg at week 3; then 900 mg every 2 weeks; OR
  - **iii.** 20 kg to < 30 kg: 600 mg weekly x 2 doses, 600 mg at week 3; then 600 mg every 2 weeks; OR
  - **iv.** 10 kg to < 20 kg: 600 mg weekly x 1 dose, 300 mg at week 2; then 300 mg every 2 weeks; OR
  - **v.** 5 kg to < 10 kg: 300 mg weekly x 1 dose, 300 mg at week 2; then 300 mg every 3 weeks.

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2. Generalized Myasthenia Gravis. 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, 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.

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.
  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.

Dosing. Approve if the dose is administered intravenously and meets ONE of the following (A or B):
A) The dose is ≤ 900 mg weekly for the first 4 weeks; OR
B) The dose is ≤ 1,200 mg every 2 weeks thereafter.

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3. 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 history 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) Patients is Currently Receiving Soliris. 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 was confirmed by 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.

Dosing. Approve if the dose is administered intravenously and meets ONE of the following (A or B):

A) The dose is ≤ 900 mg weekly for the first 4 weeks; OR

B) The dose is ≤ 1,200 mg every 2 weeks thereafter.

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4. Paroxysmal Nocturnal Hemoglobinuria. 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 ≥ 18 years of age; AND

ii. 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

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

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.

Dosing. Approve if the dose is administered intravenously and meets ONE of the following (A or B):

A) The dose is ≤ 600 mg weekly for the first 4 weeks; OR

B) The dose is ≤ 900 mg every 2 weeks thereafter.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Soliris is not recommended in the following situations:

1. 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).

2. 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.

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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Generalized Myasthenia Gravis:** Revised the Myasthenia Gravis Activities of Daily Living (MG-ADL) score to ≥ 6 to align with the prescribing information; previously it was MG-ADL ≥ 5.	05/24/2023
Early Annual Revision	**Generalized Myasthenia Gravis:** Initial therapy, for the criterion regarding evidence of unresolved symptoms of generalized myasthenia gravis, the examples of evidence of unresolved symptoms of generalized myasthenia gravis were moved to a Note. **Conditions Not Recommended for Approval:** Criterion regarding concomitant use of Soliris with a rituximab product, Enspryng, Ultomiris, or Uplizna was revised to include neonatal Fc receptor blockers. Examples of neonatal Fc receptor blockers were added as a Note.	09/20/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Complement Inhibitors – Ultomiris Intravenous Utilization Management Medical 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 medical benefit coverage of Ultomiris intravenous. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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1. Atypical Hemolytic Uremic Syndrome. Approve for 1 year if the patient meets the following (A and B):

A) Patient does not have Shiga toxin *Escherichia coli*-related hemolytic uremic syndrome; AND

B) The medication is prescribed by or in consultation with a nephrologist.

Dosing. Approve ONE of the following weight-based regimens (A or B):

A) ≥ 5 kg to < 20 kg: ≤ 600 mg administered by intravenous infusion for one dose, followed by ≤ 600 mg administered by intravenous infusion once every 4 weeks; OR

B) ≥ 20 kg: ≤ 3,000 mg administered by intravenous infusion for one dose, followed by ≤ 3,600 mg administered by intravenous infusion once every 8 weeks.

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2. Generalized Myasthenia Gravis. 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, 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 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, or 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.

B) 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.

Dosing. Approve the following dose if the patient is ≥ 40 kg: ≤ 3,000 mg administered by intravenous infusion for one dose, followed by ≤ 3,600 mg administered by intravenous infusion once every 8 weeks.

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3. Paroxysmal Nocturnal Hemoglobinuria. 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.** 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
- **ii.** The medication is prescribed by or in consultation with a hematologist.

B) Patient is Currently Receiving Ultomiris (intravenous or subcutaneous). Approve for 1 year if the patient meets the following (i and ii):
- **i.** 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.

Dosing. Approve ONE of the following weight-based regimens (A or B):

A) ≥ 5 kg to < 20 kg: ≤ 600 mg administered by intravenous infusion for one dose, followed by ≤ 600 mg administered by intravenous infusion once every 4 weeks; OR

B) ≥ 20 kg: ≤ 3,000 mg administered by intravenous infusion for one dose, followed by ≤ 3,600 mg administered by intravenous infusion once every 8 weeks.

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.

REFERENCES

1. Ultomiris® intravenous infusion and subcutaneous injection [prescribing information]. New Haven, CT: Alexion; July 2022.
2. Campistol JM, Arias M, Ariceta G, et al. An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. A consensus document. *Nefrologia*. 2015;35:421–447.
3. Genetics Home Reference. Atypical hemolytic-uremic syndrome. National Institutes of Health (NIH). Available at: https://ghr.nlm.nih.gov/condition/atypical-hemolytic-uremic-syndrome#sourcesforpage. Accessed on September 18, 2023.

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4. National Institute of Neurological Disorders and Stroke (NINDS). Myasthenia Gravis. Updated March 2020. Available at: https://www.ninds.nih.gov/sites/default/files/migrate-documents/myasthenia_gravis_e_march_2020_508c.pdf. Accessed on September 18, 2023.
5. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. *Neurology*. 2016;87:419–425.
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7. Shah N, Bhatt H. Paroxysmal nocturnal hemoglobinuria. Stat Pearls [Internet]. Treasure Island (FL): StatPearls Published; 2021 Jan. 2020 Dec 1.
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9. Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. *Neurology*. 2021 Jan 19;96(3):114-122.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/09/2022
Selected Revision	**Generalized Myasthenia Gravis:** Revised the Myasthenia Gravis Activities of Daily Living (MG-ADL) score to ≥ 6 to align with the prescribing information; previously it was MG-ADL ≥ 5.	05/24/2023
Early Annual Revision	**Generalized Myasthenia Gravis:** Initial therapy, for the criterion regarding evidence of unresolved symptoms of generalized myasthenia gravis, the examples of evidence of unresolved symptoms of generalized myasthenia gravis were moved to a Note. **Conditions Not Recommended for Approval:** Criterion regarding concomitant use of Ultomiris IV with another complement inhibitor or Vyvgart was revised to add rituximab and other neonatal Fc receptor blockers (Vyvgart Hytrulo, Rystiggo). Examples of complement inhibitors and neonatal Fc receptor blockers were moved to a Note.	09/20/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Coronavirus Disease – Evusheld Utilization Management Medical 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 history 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 clinical 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:

1. **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.

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. Evusheld™ intramuscular injections [prescribing information]. Wilmington, DE: AstraZeneca; June 2022.
2. 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.
3. 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.
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5. COVID-19 Treatment Guidelines Panel. The COVID-19 Treatment Panel's revised statement on tixagevimab plus cilgavimab (Evusheld) as pre-exposure prophylaxis of COVID-19. National Institutes of Health. January 30, 2023. Available at: https://files.covid19treatmentguidelines.nih.gov/guidelines/archive/revised-statement-on-evusheld-01-30-2023.pdf. Accessed on April 7, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	02/09/2022
Selected Revision	**Coronavirus Disease 2019 (COVID-19), Pre-Exposure Prophylaxis:** Added requirement that the patient has NOT received the full initial dose of Evusheld. Revised dosing to include initial dose of 300 mg of tixagevimab and 300 mg of cilgavimab (2 cartons of Evusheld), or for patients who have already received 150 mg of tixagevimab and 150 mg of cilgavimab (1 carton of Evusheld), approve 150 mg of tixagevimab and 150 mg of cilgavimab (1 carton of Evusheld).	03/02/2022
Selected Revision	**Coronavirus Disease 2019 (COVID-19), Pre-Exposure Prophylaxis:** Removed requirement that the patient has not previously received Evusheld. Removed requirement that the patient has previously received Evusheld and at least 6 months will elapse between previous dose and this repeat dose.	03/09/2022
Selected Revision	**Coronavirus Disease 2019 (COVID-19), Pre-Exposure Prophylaxis:** Removed requirement that the patient has NOT received the full initial dose. Revised dosing for patients who received initial dose of 150 mg of tixagevimab and cilgavimab to: 150 mg of tixagevimab and cilgavimab if initial dose received ≤ 3 months ago, or 300 mg of tixagevimab and cilgavimab if initial dose received > 3 months ago. Added repeat dosing regimen.	07/13/2022
Annual Revision	No criteria changes.	02/08/2023
Selected Revision	**Coronavirus Disease 2019 (COVID-19), Pre-Exposure Prophylaxis:** Moved condition of approval from Recommended Authorization Criteria to Conditions Not Recommended for Approval.	04/12/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Coronavirus Disease – Veklury Utilization Management Medical Policy
- Veklury® (remdesivir intravenous infusion – Gilead)

REVIEW DATE: 12/07/2022

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 with positive results of direct SARS-CoV-2 testing, who are:
- Hospitalized, or
- Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.[1]

Dosing Information

The recommended dose of Veklury, for patients:
- Weighing ≥ 40 kg, is a single 200 mg loading dose given by intravenous (IV) infusion on Day 1, followed by 100 mg once daily, starting on Day 2.[1]
- Weighing ≥ 3 kg and < 40 kg, is a single 5.0 mg/kg loading dose given by IV infusion on Day 1, followed by 2.5 mg/kg once daily, starting on Day 2.[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 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 medical benefit coverage of Veklury. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **Coronavirus Disease 2019 (COVID-19), Treatment.** Approve for the duration noted if the patient meets the following criteria (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.

   Dosing. Approve one of the following dosing regimens (A or B):
   - **A)** Patient weighs ≥ 40 kg and meets all of the following (i, ii, and iii):
     - **i.** Loading dose: 200 mg intravenous dose given once on Day 1 of therapy; AND
     - **ii.** Maintenance dose: 100 mg intravenous dose given once daily beginning on Day 2; AND
     - **iii.** Patient meets one of the following (a or b):
       - **a)** Hospitalized patient, treat for up to a total of 10 days; OR
       - **b)** Outpatient treatment, treat for a total of 3 days; OR
   - **B)** Patient weighs ≥ 3 kg and < 40 kg and meets all of the following (i, ii, and iii):
     - **i.** Loading dose: 5 mg/kg intravenous dose given on Day 1 of therapy; AND
     - **ii.** Maintenance dose: 2.5 mg/kg intravenous dose given once daily beginning on Day 2; AND
     - **iii.** Patient meets one of the following (a or b):
       - **a)** Hospitalized patient, treat for up to a total of 10 days; OR
       - **b)** Outpatient treatment, treat for a total of 3 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Veklury 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. Veklury intravenous infusion [prescribing information]. Foster City, CA: Gilead; October 2022.
2. 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 November 28, 2022.
3. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Disease Society of America Guidelines on the treatment and management of patients with COVID-19. November 21, 2022. Available at: https://www.idsociety.org/COVID19guidelines. Accessed November 28, 2022.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Coronavirus Disease 2019 (COVID-19), Treatment:** Removed the qualifier "up to" from the loading and maintenance dose recommendations.	11/17/2021
Selected Revision	**Coronavirus Disease 2019 (COVID-19), Treatment:** Revised approval duration from 10 days to "Approve for the duration noted if the patient meets the following criteria." Removed requirement that the patient is ≥ 12 years of age. Added requirement that the	01/26/2022

	patient's weight is ≥ 3.5 kg. Added "Approve for 10 days if the patient" is being treated in a hospital. Added additional option of approval that approves for 3 days if the patient is treated in an outpatient setting and the patient is at high risk of progression to severe COVID-19, according to the prescriber. Revised dosing regimen to require patient to weigh ≥ 40 kg and added treatment duration of up to a total of 10 days for hospitalized patients and a total of 3 days for outpatient treatment. Added additional treatment regimen for patients ≥ 3.5 kg and < 40 kg.	
Selected Revision	**Coronavirus Disease 2019 (COVID-19), Treatment:** Revised requirement that the patient weighs ≥ 3.5 kg to ≥ 3.0 kg. Revised dosing regimen from ≥ 3.5 kg and < 40 kg to ≥ 3.0 kg and < 40 kg.	05/11/2022
Annual Revision	No criteria changes.	12/07/2022

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Dermatology – Gene Therapy – Vyjuvek Utilization Management Medical 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.

Dosing Information

Only a healthcare professional should apply Vyjuvek either in a healthcare setting (e.g., clinic) or the home setting.[1] The recommended dose is based on age (see Table 1) and applied topically to wound(s) once weekly. It may not be possible to apply Vyjuvek to all the wounds at each treatment visit. Vyjuvek should be applied to wounds until they are closed before selecting new wound(s) to treat. Prioritize weekly treatment to previously treated wounds if they re-open. If a dose is missed, apply Vyjuvek as soon as possible and resume weekly dosing thereafter. Vyjuvek is applied to the selected wound(s) in droplets spaced evenly within the wound, approximately 1 cm x 1 cm apart. The resulting droplet pattern should loosely resemble a grid. Table 2 provides a reference dose based on wound size. A hydrophobic dressing is placed on top the Vyjuvek droplets, and a standard dressing is placed on top of the hydrophobic dressing. The wound dressing should not be changed for approximately 24 hours after Vyjuvek gel administration.

Table 1. Maximum Weekly Dose by Age.[1]

Age Range	Maximum Weekly Dose	Maximum Weekly Volume*
≥ 6 months to < 3 years	1.6×10^9 PFUs	0.8 mL
≥ 3 years	3.2×10^9 PFUs	1.6 mL

* Maximum weekly volume after mixing Vyjuvek biological suspension with excipient gel; PFUs – Plaque forming units.

Table 2. Reference Dose by Wound Size.[1]

Area	Dose	Volume
< 20 cm^2	4×10^8 PFUs	0.2 mL
≥ 20 cm^2 to < 40 cm^2	8×10^8 PFUs	0.4 mL
≥ 40 cm^2 to ≤ 60 cm^2	1.2×10^9 PFUs	0.6 mL

PFUs – Plaque forming units.

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 history, 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 medical benefit coverage of Vyjuvek. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **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.

Dosing. Approve one of the following dosing regimens (A or B):

A) Patient is ≥ 6 months to < 3 years of age: Approve up to 0.8 mL (1.6×10^9 plaque forming units) topically once weekly. Note: This is the maximum weekly volume after mixing Vyjuvek biological suspension with excipient gel.

B) Patient is ≥ 3 years of age: Approve up to 1.6 mL (3.2×10^9 plaque forming units) topically once weekly. Note: This is the maximum weekly volume after mixing Vyjuvek biological suspension with excipient gel.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vyjuvek 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. Vyjuvek™ biological suspension [prescribing information]. Pittsburgh, PA: Krystal Biotech; May 2023.
2. 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.
3. Payne AS. Topical gene therapy for epidermolysis bullosa. *N Engl J Med.* 2022;387(24):2281-2284.
4. 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.
5. 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.
6. 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	06/28/2023
Selected Revision	**Dystrophic Epidermolysis Bullosa.** Criteria were divided into "Initial Therapy" and "Patient is Currently Receiving Vyjuvek". The approval duration for initial and continuation therapy are 3 months, previously criteria approved all patients for 6 months. Initial Therapy A documentation requirement was added to criteria for the confirmation of the diagnosis by genetic testing showing a pathogenic mutation in the collagen type VII alpha 1 chain (COL7A1) gene. A documentation requirement was added to criteria for one clinical feature of dystrophic epidermolysis bullosa. Criteria for one or more open wound(s) were clarified to address such wound(s) would be treated (referred to as "target wound[s]") and that, according to the prescriber, the target wound(s) meets all of the following criteria: is clean in appearance and does not appear to be infected, has adequate granulation tissue and vascularization, and squamous cell carcinoma has been ruled out. Patient is Currently Receiving Vyjuvek on Previously Treated Wound(s) Patients currently receiving Vyjuvek on previously treated wounds are required to have a target wound(s) that remains open, according to the prescriber and has decreased in size from baseline as demonstrated by wound measurements or photographs, according to the prescriber. The medication must also be prescribed by or in consultation with a dermatologist or wound care specialist with expertise in the management of dystrophic epidermolysis bullosa. Of note, if the patient is treating a new wound(s) not previously treated with Vyjuvek or reopened recurrent wound(s) the patient is directed to Initial Therapy criteria.	09/13/2023
Selected Revision	**Dystrophic Epidermolysis Bullosa.** Initial Therapy: The approval duration was changed to 6 months. Patient is Currently Receiving Vyjuvek on Previously Treated Wound(s): The approval duration was changed to 6 months.	09/27/2023
Selected Revision	**Dystrophic Epidermolysis Bullosa.** Patient is Currently Receiving Vyjuvek on Previously Treated Wound(s): The criterion requiring that the target wound(s) has decreased in size from baseline as demonstrated by wound measurements or photographs, according to the prescriber was modified to remove the requirement of wound measurements or photographs. The criterion now requires that according to the prescriber, the target wound(s) has decreased in size from baseline.	10/11/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Diabetes – Tzield Utilization Management Medical Policy
- Tzield™ (teplizumab-mzwv intravenous infusion – Provention/Sanofi)

REVIEW DATE: 11/30/2022

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.

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 (2022) comment on available data with Tzield but do not make recommendations regarding its use.[3] According to the ADA Standards, screening for pre-symptomatic type 1 diabetes using screening tests that detect autoantibodies to insulin, glutamic acid decarboxylase (GAD), islet antigen 2, or zinc transporter 8 is currently recommended in the setting of a research study or can be considered as an option for first-degree family members of a proband with type 1 diabetes (Level B recommendation).[3] Development of and persistence of multiple islet autoantibodies is a risk factor for clinical diabetes and may serve as an indication for intervention in the setting of a clinical trial or screening for Stage 2 type 1 diabetes (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 new-onset hyperglycemia and 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); glycosylated hemoglobin (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 or 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}.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Tzield. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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1. **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 criteria (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 both of the following (i and ii) **[documentation required]**:
- **i.** Patient has taken an oral glucose tolerance test within the preceding 2 months; AND
- **ii.** The results of the oral glucose tolerance test indicated dysglycemia by meeting at least one of the following (a, b, or c):
  - **a)** Fasting plasma glucose level ≥ 110 to < 126 mg/dL; OR
  - **b)** 2-hour postprandial plasma glucose level ≥ 140 to < 200 mg/dL; OR
  - **c)** Intervening postprandial glucose level at 30, 60, or 90 minutes > 200 mg/dL; 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 history 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.

Dosing. Approve a one-time, 14-day course of Tzield with the following regimen (A, B, C, D, and E):

A) 65 mcg/m^2 body surface area (BSA) given intravenously on Day 1; AND
B) 125 mcg/m^2 BSA given intravenously on Day 2; AND
C) 250 mcg/m^2 BSA given intravenously on Day 3; AND
D) 500 mcg/m^2 BSA given intravenously on Day 4; AND
E) 1,030 mcg/m^2 BSA given intravenously once daily on Days 5 through 14.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tzield is not recommended in the following situations:

1. **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).

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. Tzield™ intravenous infusion [prescribing information]. Red Bank, NJ: Provention; November 2022.
2. Herold KC, Bundy BN, Long SA, et al; Type 1 Diabetes TrialNet Study Group. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. *N Engl J Med*. 2019 Aug 15;381(7):603-613.
3. American Diabetes Association. Standards of medical care in diabetes – 2022. *Diabetes Care*. 2022;45(Suppl 1):S1-S258.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	11/30/2022

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Elaprase Utilization Management Medical 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 medical benefit coverage of Elaprase. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **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.

Dosing. Each dose must not exceed 0.5 mg/kg administered intravenously no more frequently than once a week.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Elaprase 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. Elaprase® intravenous infusion [prescribing information]. Lexington, MA: Shire Human Genetic Therapies; October 2021.
2. 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.
3. Muenzer J, Beck M, Eng CM, et al. Multidisciplinary management of Hunter syndrome. *Pediatrics*. 2009;124:e1228-e1239.
4. 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.
5. D'Avanzo F, Rigon L, Zanetti A, Tomanin R. Mucopolysaccharidosis type II: One hundred years of research, diagnosis, and treatment. *Int J Mol Sci*. 2020;21:E1258.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/06/2022
Annual Revision	No criteria changes.	04/12/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Elfabrio Utilization Management Medical 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. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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1. **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.

   Dosing. Each dose must not exceed 1 mg/kg administered intravenously no more frequently than once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Elfabrio is not recommended in the following situations:

1. **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.

2. **Concurrent Use with Fabrazyme (agalsidase beta intravenous infusion).**

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

1. Elfabrio® intravenous infusion [prescribing information]. Parma, Italy: Chiesi; May 2023.
2. Schiffmann R. Fabry Disease. *Handb Clin Neurol*. 2015;132:231-248.
3. 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.
4. 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.
5. Spada M, Pagliardini S, Yasuda M, Tukel T, Thiagarajan G, Sakuraba H, Ponzone A, Desnick RJ. High incidence of later-onset fabry disease revealed by newborn screening. *Am J Hum Genet*. 2006 Jul;79(1):31-40.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	-	06/14/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Fabrazyme Utilization Management Medical 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 medical benefit coverage of Fabrazyme. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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1. **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.

   Dosing. Each dose must not exceed 1 mg/kg administered intravenously no more frequently than once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Fabrazyme 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. Fabrazyme® intravenous infusion [prescribing information]. Cambridge, MA: Genzyme; March 2021.
2. Schiffmann R. Fabry Disease. *Handb Clin Neurol*. 2015;132:231-248.
3. 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.
4. 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/06/2022
Annual Revision	No criteria changes.	04/12/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Kanuma Utilization Management Medical 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 medical benefit coverage of Kanuma. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **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.

Dosing. Each dose must not exceed 5 mg/kg administered intravenously no more frequently than once per week.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kanuma 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. Kanuma® intravenous infusion [prescribing information]. Cheshire, CT: Alexion; November 2021.
2. 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.
3. Erwin AL. The role of sebelipase alfa in the treatment of lysosomal acid lipase deficiency. *Ther Adv Gastroenterol*. 2017;10:553-562.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Lysosomal Acid Lipase Deficiency:** The dosing limit was increased from 3 mg/kg to 5 mg/kg due to revisions in the prescribing information.	04/06/2022
Annual Revision	No criteria changes.	04/12/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Lamzede Utilization Management Medical 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*.[6] 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.

Dosing Information

The recommended dosage of Lamzede is 1 mg/kg (actual body weight) administered once every week as an intravenous infusion.[1] The total volume of infusion is determined by the patient's actual body weight and should be administered over a minimum of 60 minutes for patients weighing up to 49 kg. Patients weighing ≥ 50 kg should be infused at a maximum infusion rate of 25 mL/hour to control the protein load.

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 medical benefit coverage of Lamzede. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. 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 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.
- **C)** Patient has biallelic pathogenic variants in Mannosidase Alpha Class 2B Member 1 (*MAN2B1)* as confirmed by mutation testing; AND
- **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.

Dosing. Approve up to 1 mg/kg (actual body weight) administered by intravenous infusion no more frequently than every week.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lamzede 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. Lamzede® intravenous infusion [prescribing information]. Cary, NC: Chiesi USA; February 2023.

2. 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.
3. Data on file. Lamzede summary of studies evaluating safety and efficacy of velmanase alpha. Cheisi USA; received February 20, 2023.
4. 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.
5. 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.
6. 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	03/08/2023
Selected Revision	**Alpha-mannosidosis:** The following criteria was added "Patient has biallelic pathogenic variants in Mannosidase Alpha Class 2B Member 1 (*MAN2B1)* as confirmed by mutation testing."	03/22/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Mepsevii Utilization Management Medical 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 medical benefit coverage of Mepsevii. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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1. 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.

Dosing. Each dose must not exceed 4 mg/kg administered intravenously no more frequently than once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mepsevii 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. Mepsevii® intravenous infusion [prescribing information]. Novato, CA: Ultragenyx; December 2020.
2. Montano AM, Lock-Hock N, Steiner RD, et al. Clinical course of sly syndrome (mucopolysaccharidosis type VII). *J Med Genet*. 2016;53:403-418.
3. 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/06/2022
Annual Revision	No criteria changes.	04/12/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Naglazyme Utilization Management Medical 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 medical benefit coverage of Naglazyme. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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1. 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.

Dosing. Each dose must not exceed 1 mg/kg administered intravenously no more frequently than once weekly.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Naglazyme 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. Naglazyme® intravenous infusion [prescribing information]. Novato, CA: BioMarin; April 2020.
2. Harmatz PR, Shediac R. Mucopolysaccharidosis VI: Pathophysiology, diagnosis and treatment. *Front Biosci*. 2017;22:385-406.
3. Vairo F, Federhen A, Baldo G, et al. Diagnostic and treatment strategies in mucopolysaccharidosis VI. *Appl Clin Genet*. 2015;8:245-255.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/06/2022
Annual Revision	No criteria changes.	04/12/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Revcovi Utilization Management Medical Policy
- Revcovi® (elapegademase-lvlr intramuscular injection – Leadiant)

REVIEW DATE: 11/16/2022

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), 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.[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.

Dosing Considerations

Dosing is provided in the Prescribing Information for patients who are naïve to Adagen® (pegademase bovine injection for intramuscular use), as well as for patients who are Adagen-experienced.[1] For Adagen-naïve patients, the starting weekly dose of Revcovi is 0.4 mg/kg (divided into two doses) by intramuscular route. This dose is continued for at least 12 to 24 weeks until immune reconstitution is achieved.

Thereafter, the dose may be gradually adjusted down for maintenance (adjusted based on laboratory values). Lower starting doses are generally recommended for Adagen-experienced patients; the Prescribing Information provides a conversion factor for calculating the Revcovi dose based on the prior Adagen dose. The Prescribing Information notes that the optimal long-term dose and schedule of administration are individualized; total weekly doses may be divided into multiple intramuscular injections during a week. The dosing provided in this policy is intended to provide a sufficient maximum weekly dose for the majority of patients; exceptions will be reviewed by a clinician on a case-by-case basis.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Revcovi. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID).** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient has a diagnosis of ADA-SCID confirmed by one of the following criteria (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 who specializes in ADA-SCID or related disorders.

   Dosing. Approve up to a maximum weekly dose of 0.4 mg/kg by intramuscular route.
   Note: Doses may be divided into multiple injections as long as weekly cumulative maximum of 0.4 mg/kg is not exceeded.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Revcovi 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. Revcovi® [prescribing information]. Gaithersburg, MD: Leadiant Biosciences; December 2020.
2. Hershfield M. GeneReviews [Internet]. Updated March 16, 2017. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1483/. Accessed on November 8, 2022.
3. Gaspar HB, Aiuti A, Porta F, et al. How I treat ADA deficiency. *Blood*. 2009;114:3524-3532.
4. 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/10/2021
Annual Revision	No criteria changes.	11/16/2022

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Vimizim Utilization Management Medical 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 medical benefit coverage of Vimizim. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **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.

   Dosing. Approve up to 2 mg/kg of body weight administered intravenously no more frequently than once a week.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vimizim 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. Vimizim® intravenous infusion [prescribing information]. Novato, CA: BioMarin; January 2021.
2. 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.
3. Tomatsu S, Yasuda E, Patel P, et al. Morquio A syndrome: Diagnosis and current and future therapies. *Pediatr Endocrinol Rev*. 2014;12:141-151.
4. Regier DS, Tanpaiboon P. Role of elosulfase alfa in mucopolysaccharidosis IVA. *Appl Clin Genet*. 2016;9:67-74.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/06/2022
Annual Revision	No criteria changes.	04/12/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Xenpozyme Utilization Management Medical 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.

Dosing Information

Dosing is weight-based.[1] For patients with a body mass index (BMI) of ≤ 30 kg/m^2, actual body weight is used. For patients with a BMI > 30 kg/m^2 adjusted body weight is used (adjusted body weight in kg = [actual height in meters]^2 x 30). Home infusion of Xenpozyme under the supervision of a healthcare provider may be considered for patients on a maintenance dose and who are tolerating the infusion well. The decision to have patients moved to home infusion should be made after evaluation and recommendation by a physician.

The recommended starting dose in adults is 0.1 mg/kg via intravenous (IV) infusion.[1] The dose is titrated every 2 weeks over a period of 14 weeks to a maintenance dose of 3 mg/kg every 2 weeks (Table 1). In pediatric patients, the recommended starting dose is 0.03 mg/kg via IV infusion. The dose is titrated every 2 weeks over a period of 16 weeks to a maintenance dose of 3 mg/kg every 2 weeks (Table 2). To reduce the risk of hypersensitivity and infusion-related reactions or elevated transaminase levels, the dose escalation regimen outlined in Tables 1 and 2 below should be followed. A dose is considered "missed" when it is not administered within 3 days of the scheduled date. Refer to Table 3 for missed doses.

Table 1. Xenpozyme Dose Escalation Regimen for Adults (≥ 18 Years of Age).[1]

First dose (Day 1/Week 0)	0.1 mg/kg
Second dose (Week 2)	0.3 mg/kg
Third dose (Week 4)	0.3 mg/kg
Fourth dose (Week 6)	0.6 mg/kg
Fifth dose (Week 8)	0.6 mg/kg
Sixth dose (Week 10)	1 mg/kg
Seventh dose (Week 12)	2 mg/kg
Eighth dose (Week 14)†	3 mg/kg

† The dose escalation phase includes the first 3 mg/kg dose.

Table 2. Xenpozyme Dose Escalation Regimen for Pediatric Patients.[1]

First dose (Day 1/Week 0)	0.03 mg/kg
Second dose (Week 2)	0.1 mg/kg
Third dose (Week 4)	0.3 mg/kg
Fourth dose (Week 6)	0.3 mg/kg
Fifth dose (Week 8)	0.6 mg/kg
Sixth dose (Week 10)	0.6 mg/kg
Seventh dose (Week 12)	1 mg/kg
Eighth dose (Week 14)†	2 mg/kg
Ninth dose (Week 16) †	3 mg/kg

† The dose escalation phase includes the first 3 mg/kg dose.

Table 3. Dosing Recommendations for Xenpozyme Missed Doses*.[1]

Consecutive Missed Doses In:	Escalation Phase	Maintenance Phase
1 missed dose	First dose after a missed dose: Administer last tolerated dose. Second and subsequent doses after missed dose: Resume dose escalation at next infusion according to Table 1 for adult patients or Table 2 for pediatric patients.	First and subsequent doses after missed dose: Administer maintenance dose.
2 consecutive missed doses	First dose after missed dose: Administer 1 dose below the last tolerated dose. Second and subsequent doses after missed dose: Resume dose escalation according to Table 1 for adults or Table 2 for pediatric patients.	First dose after missed dose: Administer 1 dose below the maintenance dose. Second and subsequent doses after missed dose: Resume the maintenance dose.
≥ 3 consecutive missed doses	First and subsequent doses after missed doses: Resume dose escalation at 0.3 mg/kg and follow Table 1 for adults or Table 2 for pediatric patients.	First and subsequent doses after missed doses: Restart dosing at 0.3 mg/kg and follow Table 1 for adult patients or Table 2 for pediatric patients.

*At scheduled infusion after a missed dose, if the dose administered is 0.3 mg/kg or 0.6 mg/kg, administer that dose twice as per Table 1 and 2.

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 medical benefit coverage of Xenpozyme. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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1. **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.

Dosing. Approve up to 3 mg/kg administered by intravenous infusion no more frequently than once every 2 weeks.
Note: For patients with a body mass index (BMI) of ≤ 30 kg/m^2, actual body weight is used. For patients with a BMI > 30 kg/m^2 adjusted body weight is used. To calculate adjusted body weight, use the following equation: adjusted body weight in kg = (actual height in meters)^2 x 30.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xenpozyme is not recommended in the following situations:

1. **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]

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. Xenpozyme™ intravenous infusion [prescribing information]. Cambridge, MA: Genzyme; August 2022.
2. Wasserstein M, Lachmann R, Hollack C, et al. A randomized, placebo-controlled clinical trial evaluating olipudase alfa enzyme replacement for chronic acid sphingomyelinase deficiency (ASMD) in adults: One-year results. *Genet Med*. 2022;24(7):1425-1436.
3. Diaz GA, Jones SA, Scarpa M, et al. One-year results of a clinical trial of olipudase alfa enzyme replacement therapy in pediatric patients with acid sphingomyelinase deficiency. *Genet Med.* 2021;23:154-1550.
4. Geberhiwot, T., Wasserstein, M., Wanninayake, S. et al. Consensus clinical management guidelines for acid sphingomyelinase deficiency (Niemann–Pick disease types A, B and A/B). *Orphanet J Rare Dis* 18, 85 (2023). Available at: https://doi.org/10.1186/s13023-023-02686-6. Accessed on: August 31, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Selected Revision	**Acid Sphingomylinase Deficiency (ASMD).** Criteria for the diagnosis of ASMD were expanded to additionally require that the diagnosis be confirmed by mutation testing and that Gaucher disease be excluded as a diagnosis. Previously, the diagnosis was required to be established by enzymatic assay alone. Criteria requiring patients have AMSD type B or A/B was revised to clarify that patients have two or more non-central nervous system sign of ASMD type B or type A/B, examples of non-central nervous system signs were moved to a note.	11/09/2022
Annual Revision	No criteria changes.	09/13/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Gamifant Utilization Management Medical Policy
- Gamifant® (emapalumab-lzsg intravenous infusion – Sobi)

REVIEW DATE: 01/04/2023

OVERVIEW

Gamifant, an anti-interferon gamma (IFN-γ) antibody, is indicated for the treatment of adult and pediatric patients with **primary hemophagocytic lymphohistiocytosis** (HLH) 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 must 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 medical benefit coverage of Gamifant. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 in those who meet the following criteria:

FDA-Approved Indication

1. **Hemophagocytic Lymphohistiocytosis, Primary.** Approve Gamifant for 6 months if the patient meets the following criteria (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;
       - **b)** Splenomegaly;
       - **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;
         - **3)** Neutrophils < 1.0 x 10^9/L;
       - **d)** Patient meets one of the following (1 or 2):
         - **1)** Fasting triglycerides ≥ 265 mg/dL; OR
         - **2)** Fibrinogen ≤ 1.5 g/L;
       - **e)** Hemophagocytosis in bone marrow, spleen, or lymph nodes;
       - **f)** Low or absent natural killer cell activity (according to local laboratory reference);
       - **g)** Ferritin ≥ 500 mcg/L;
       - **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.

   Dosing. Approve up to a maximum dose of 10 mg/kg by intravenous infusion, not more frequently than twice weekly (once every 3 to 4 days).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Gamifant 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. Gamifant® intravenous infusion [prescribing information]. Waltham, MA: Sobi; November 2018.
2. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood*. 2011;118(15):4041-4052.
3. Weitzman S. Approach to hemophagocytic syndromes. *Hematology Am Soc Hematol Edu Program.* 2011;2011:178-183.
4. Avau A, Matthys P. Therapeutic potential of interferon-γ and its antagonists in autoinflammation: lessons from murine models of systemic juvenile idiopathic arthritis and macrophage activation syndrome. *Pharmaceuticals.* 2015;8:793-815.
5. Osinska I, Popko K, Demkow U. Perforin: an important player in immune response. *Centr Eur J Immunol*. 2014;39(1):109-115.
6. Henter J, Horne A, Aricó M, et al. HLH-2004: Diagnostic and Therapeutic Guidelines for Hemophagocytic Lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48:124-131.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	12/22/2021
Annual Revision	No criteria changes.	01/04/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Gaucher Disease – Enzyme Replacement Therapy – Cerezyme Utilization Management Medical 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 medical benefit coverage of Cerezyme. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **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.

   Dosing. Each individual dose must not exceed 60 U/kg administered intravenously no more frequently than three times per week.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cerezyme 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. Cerezyme® intravenous infusion [prescribing information]. Cambridge, MA: Genzyme; January 2022.
2. Burrow TA, Barnes S, and Grabowski GA. Prevalence and management of Gaucher disease. *Pediatric Health Med Ther*. 2011;2:59-73.
3. Cox T. Gaucher disease: clinical profile and therapeutic development. *Biologics*. 2010;4:299-313.
4. Jmoudiak, M. and Futerman, AH. Gaucher disease: Pathological mechanisms and modern management. *Br J Haematol*. 2005;129(2):178–188.
5. Grabowski GA. Lysosomal storage disease 1- phenotype, diagnosis, and treatment of Gaucher's disease. *Lancet*. 2008;372:1263-1271.
6. Zimran A. How I treat Gaucher disease. *Blood*. 2011;118:1463-1471.
7. 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.
8. Baris HN, Cohen IJ, Mistry PK. Gaucher disease: The metabolic defect, pathophysiology, phenotypes and natural history. *Pediatr Endocrinol Rev*. 2014;12:72-81.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	03/16/2022
Annual Revision	No criteria changes.	04/05/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Gaucher Disease – Enzyme Replacement Therapy – Elelyso Utilization Management Medical 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 and older 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 medical benefit coverage of Elelyso. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **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)** Patient 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.

   Dosing. Each individual dose must not exceed 60 U/kg administered intravenously no more frequently than once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Elelyso 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. Elelyso® intravenous infusion [prescribing information]. New York, NY: Pfizer; July 2021.
2. Burrow TA, Barnes S, and Grabowski GA. Prevalence and management of Gaucher disease. *Pediatric Health Med Ther*. 2011;2:59-73.
3. Cox T. Gaucher disease: clinical profile and therapeutic development. *Biologics*. 2010;4:299-313.
4. Jmoudiak, M. and Futerman, AH. Gaucher disease: Pathological mechanisms and modern management. *Br J Haematol*. 2005;129(2):178–188.
5. Grabowski GA. Lysosomal storage disease 1- phenotype, diagnosis, and treatment of Gaucher's disease. *Lancet*. 2008;372:1263-1271.
6. Zimran A. How I treat Gaucher disease. *Blood*. 2011;118:1463-1471.
7. 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.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	03/16/2022
Annual Revision	No criteria changes.	04/05/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Gaucher Disease – Enzyme Replacement Therapy – Vpriv Utilization Management Medical 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 medical benefit coverage of Vpriv. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **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.

   Dosing. Each individual dose must not exceed 60 U/kg administered intravenously no more frequently than once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vpriv 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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	03/16/2022
Annual Revision	No criteria changes.	04/05/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Gonadotropin-Releasing Hormone Agonists – Central Precocious Puberty Utilization Management Medical 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]

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]

Dosing Information

Fensolvi is administered by a subcutaneous injection and both Lupron Depot-Ped and Triptodur are administered by intramuscular injection.[1-3] Fensolvi is administered once every 6 months, Lupron Depot-Ped is administered once a month, once every 3 months (12 weeks), or once every 6 months (24 weeks), and Triptodur is administered once every 24 weeks. There are no specific dosing recommendations for off-label use of Fensolvi, Lupron Depot-Ped, or Triptodur. Therefore, the FDA-approved dosing in the product labeling for approved uses has been cited for off-label uses. Treatment decisions, including duration of therapy, are individualized with careful consideration of the risks and benefit of the selected regimen.

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 medical benefit coverage of the gonadotropin-releasing hormone agonists (Fensolvi, Lupron Depot-Ped, and Triptodur). Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 gender-dysphoric/gender-incongruent patients treated with Fensolvi, Lupron Depot-Ped, or Triptodur, as well as the monitoring requested 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

1. Central Precocious Puberty. Approve for 1 year.

Dosing. Approve one of the following dosing regimens (A, B, or C):

A) Fensolvi: Approve up to one injection (45 mg) given subcutaneously once every 6 months; OR

B) Lupron Depot-Ped: Approve ONE of the following doses (i, ii, iii, iv, or v); OR

- **i.** 1-month depot, ≤ 25 kg: Approve up to one 1-month depot (7.5 mg) given intramuscularly (IM) once every month; OR
- **ii.** 1-month depot, > 25 to 37.5 kg: Approve up to one 1-month depot (11.25 mg) given IM once every month; OR
- **iii.** 1-month depot, > 37.5 kg: Approve up to one 1-month depot (15 mg) given IM once every month; OR
- **iv.** 3-month depot: Approve up to one 3-month depot (11.25 mg or 30 mg) given IM once every 3 months (12 weeks); OR
- **v.** 6-month depot: Approve up to one 6-month depot (45 mg) given IM once every 6 months (24 weeks).

C) Triptodur: Approve up to one injection (22.5 mg) given IM once every 24 weeks.

Other Uses with Supportive Evidence

2. Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Gender Reassignment (Female-to-Male or Male-to-Female). Approve for 1 year if prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of transgender patients.

Dosing. Approve ONE of the following dosing regimen (A, B, or C):

A) Fensolvi: Approve up to one injection (45 mg) given subcutaneously once every 6 months; OR

B) Lupron Depot-Ped: Approve ONE of the following doses (i, ii, or iii); OR

i. 1-month depot: Approve up to one 1-month depot (7.5 mg, 11.25 mg, or 15 mg) given intramuscularly (IM) once every month; OR
ii. 3-month depot: Approve up to one 3-month depot (11.25 mg or 30 mg) given IM once every 3 months (12 weeks); OR
iii. 6-month depot: Approve up to one 6-month depot (45 mg) given IM once every 6 months (24 weeks).

C) Triptodur: Approve up to one injection (22.5 mg) given IM once every 24 weeks.

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:

1. **Peripheral Precocious Puberty (Also Known As GnRH-Independent Precocious 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]).

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. Lupron Depot-Ped® [prescribing information]. North Chicago, IL; AbbVie; April 2023.
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3. Fensolvi® [prescribing information]. Fort Collins, CO: Tolmar; April 2023.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/02/2022
Annual Revision	Lupron Depot-Ped dosage (for each indication): Updated frequency to also include 12 weeks on the 3-month depot. Added the following dosage regimen: 6-month depot: Approve up to one 6-month depot (45 mg) given IM once every 6 months (24 weeks).	11/08/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Gonadotropin-Releasing Hormone Agonists – Implants Utilization Management Medical 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) agonists 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 that of 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 medical benefit coverage of Supprelin LA, Vantas, and Zoladex. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. 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 use in children with central precocious puberty, it does not need to be prescribed by or in consultation with a specialist.

Automation: None.

*Indications and/or approval conditions noted with **[eviCore]** are managed by eviCore healthcare for those clients who use eviCore for oncology and/or oncology-related reviews. For these conditions, a prior authorization review should be directed to eviCore at www.eviCore.com.*

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.

Dosing. Approve one implant (50 mg) once every 12 months (inserted subcutaneously in the upper arm).

II. Coverage of Vantas is recommended in patients who meet one of the following criteria:

FDA-Approved Indication

1. Prostate Cancer. ***[eviCore].*** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

Dosing. Approve one implant (50 mg) once every 12 months (inserted subcutaneously in the upper arm).

Other Uses with Supportive Evidence

1. **Central Precocious Puberty.** Approve for 1 year.

   Dosing. Approve one implant (50 mg) once every 12 months (inserted subcutaneously in the upper arm).

III. Coverage of Zoladex is recommended in patients who meet one of the following criteria:

FDA-Approved Indications

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1. **Abnormal Uterine Bleeding.** Approve 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 health care practitioner who specializes in the treatment of women's health.

   Dosing. Approve Zoladex 3.6 mg implant once every 28 days (inserted subcutaneously into the anterior abdominal wall).

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2. **Breast Cancer**. ***[eviCore].*** Approve for 1 year if the patient meets the following conditions (A and B):
   A) Zoladex is used in premenopausal or perimenopausal women; AND
   B) The medication is prescribed by or in consultation with an oncologist.

   Dosing. Approve Zoladex 3.6 mg implant once every 28 days (inserted subcutaneously into the anterior abdominal wall).

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3. **Endometriosis.** Approve 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 health care practitioner who specializes in the treatment of women's health.

   Dosing. Approve Zoladex 3.6 mg implant once every 28 days (inserted subcutaneously into the anterior abdominal wall).

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4. **Prostate Cancer**. ***[eviCore].*** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

   Dosing. Approve ONE of the following dosage regimens (inserted subcutaneously into the anterior abdominal wall) [A or B]:
   A) Zoladex 3.6 mg implant once every 28 days; OR
   B) Zoladex 10.8 mg implant once every 12 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Supprelin LA, Vantas, and Zoladex is not recommended in the following situations:

1. **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.

REFERENCES

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10. American Society of Health System Pharmacists (ASHP). ASHP current drug shortages. September 24, 2021. Available at: Drug Shortage Detail: Histrelin Implant (ashp.org). Access on February 2, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Abnormal Uterine Bleeding and Endometriosis: removal of the wording "up to" and "total" from approval durations. Removal of the wording "up to" in all dosing sections.	02/16/2022
Annual Revision	No criteria changes.	02/15/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Gonadotropin-Releasing Hormone Agonists – Injectable Long-Acting Products Utilization Management Medical Policy
- Lupron Depot® (leuprolide acetate suspension for intramuscular injection – AbbVie)
- Lupaneta Pack® (leuprolide acetate for depo 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 the 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 and 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 pubery 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 therefor, 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 medical benefit coverage of Lupron Depot and Lupaneta Pack. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria. 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. 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.

*Indications and/or approval conditions noted with **[eviCore]** apply to Lupron Depot only and are managed by eviCore healthcare for those clients who use eviCore for oncology and/or oncology-related reviews. For these conditions, a prior authorization review should be directed to eviCore at www.eviCore.com. Indications and/or approval conditions for Lupaneta Pack should not be directed to eviCore.*

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lupron Depot or Lupaneta Pack are recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Endometriosis. Approve Lupron Depot 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).

Dosing. Approve one of the following dosing regimens (A or B):

- **A)** For Lupaneta Pack: Approve one of the following dosage regimens (i or ii):

i. 3.75 mg IM once every month with norethindrone 5 mg orally once daily; OR
ii. 11.25 mg IM once every 3 months with norethindrone 5 mg orally once daily; OR

B) For Lupron Depot: Approve one of the following dosage regimens (i or ii):
i. 3.75 mg IM once every month; OR
ii. 11.25 mg IM once every 3 months.

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2. Prostate Cancer. ***[eviCore]*** Approve Lupron Depot for 1 year if prescribed by or in consultation with, an oncologist.

Dosing. Approve one of the following dosing regimens (A, B, C, or D):
A) 45 mg IM once every 6 months; OR
B) 30 mg IM once every 4 months; OR
C) 22.5 mg IM once every 3 months; OR
D) 7.5 mg IM once every month.

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3. Uterine Leiomyomata (fibroids). Approve Lupron Depot for 3 months.

Dosing. Approve one of the following dosing regimens (A or B):
A) 3.75 mg IM once every month; OR
B) 11.25 mg IM once every 3 months.

Other Uses with Supportive Evidence

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4. Abnormal Uterine Bleeding. Approve Lupron Depot for 6 months.

Dosing. Approve one of the following dosage regimens (A or B):
A) 3.75 IM once every month; OR
B) 11.25 IM once every 3 months.

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5. Breast Cancer. ***[eviCore]*** Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

Dosing. Approve one of the following dosage regimens (A or B):
A) 3.75 mg IM once every month; OR
B) 11.25 mg IM once every 3 months.

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6. Gender Dysphoric/Gender-Incongruent Persons; Persons 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.

Dosing. Approve one of the following dosage regimens (A, B, C, or D):
A) 3.75 or 7.5 mg IM once every month; OR
B) 11.25 or 22.5 mg IM once every 3 months; OR

C) 30 mg IM once every 4 months; OR
D) 45 mg IM once every 6 months.

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7. Head and Neck Cancer – Salivary Gland Tumors. ***[eviCore]*** Approve Lupron Depot 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.

Dosing. Approve one of the following dosage regimens (A or B):
A) 3.75 mg or 7.5 mg IM every month; OR
B) 11.25 mg or 22.5 mg IM once every 3 months.

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8. Ovarian Cancer. ***[eviCore]*** Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

Dosing. Approve one of the following dosage regimens (A or B):
A) 3.75 mg or 7.5 mg IM once every month; OR
B) 11.25 mg or 22.5 mg IM once every 3 months

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9. Preservation of Ovarian Function/Fertility in Patients undergoing Chemotherapy. ***[eviCore]*** Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

Dosing. Approve one of the following dosage regimens (A or B):
A) 3.75 mg IM once every month; OR
B) 11.25 mg IM once every 3 months.

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10. 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). ***[eviCore]*** Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

Dosing. Approve one of the following dosage regimens (A or B):
A) 3.75 mg IM once every month; OR
B) 11.25 mg IM once every 3 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lupron Depot and Lupaneta Pack is not recommended in the following situations:

1. Hirsutism. The Endocrine Society guidelines on the treatment of hirsutism in premenopausal women (2008) 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]

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2. **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]

3. **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.

4. **Polycystic Ovarian Syndrome (PCOS)**. Review articles[24,25] do not recommend GnRH agonists as a treatment modality. Additionally, the International Evidence-based Guideline for the Assesment and Management of Polycystic Ovary Syndrome (2018) only mention GnRH products as they relate to infertility and assisted reproductive technology procedures.[26]

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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HISTORY

Type of Revision	Summary of Changes	Review Date
Selected revision	**Uterine leiomyomata (fibroids)**: Lupron Depot 3.75 mg and 11.25 mg – Approval duration is changed from 6 months to 3 months due to revised labeling.	3/03/2021
Annual revision	**Prophylaxis or Treatment of Uterine Bleeding in Patients with Hematologic Malignancy, or Undergoing Cancer Treatment, or Prior to Bone Marrow/Stem Cell Transplantation (BMT/SCT):** added or Menstrual Suppression. Removed the wording "up to" in all dosage criteria. **Ovarian Cancer:** added 7.5 mg once monthly and 22.5 mg every 3 months in dosage criteria.	2/16/2022
Annual revision	**Head and Neck Cancer – Salivary Gland Tumors**: "Patient has advanced salivary gland tumors with distant metastases" was reworded to "Patient has recurrent, unresectable, or metastatic disease." Also, coverage of strengths 3.75 mg and 11.25 mg were added for this diagnosis.	2/22/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Gout – Krystexxa Utilization Management Medical 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 medical benefit coverage of Krystexxa. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 history 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.

Dosing. Approve 8 mg as an intravenous infusion every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Krystexxa is not recommended in the following situations:

1. **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.

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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	05/04/2022
Selected Revision	**Gout, Chronic: Initial Therapy.** The requirement for current symptoms of gout was changed to require at least one tophus OR a history of 2 previous flares in the past year (prior to the current flare). Criterion requiring a 3-month trial of at least one of allopurinol, Uloric, or a uricosuric agent was changed to separate criteria to require a 3-month trial of both a xanthine oxidase inhibitor and a uricosuric agent. Notes were added to both criterion to give examples of each. **Initial Therapy and Continuation of Therapy.** Criteria were added to require: Krystexxa will be used in combination with either methotrexate, leflunomide, or azathioprine; and Krystexxa will not be used with another uric acid lowering drug with a Note providing examples. **Nephrolithiasis and/or Gouty Nephropathy:** The condition and criteria were removed from the Other Uses with Supportive Evidence section of the policy.	11/09/2022
Annual Revision	No criteria changes.	05/17/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Cablivi Utilization Management Medical 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 medical benefit coverage of Cablivi. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for one course of treatment. 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. 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 long-term efficacy, approval requires Cablivi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indication

1. 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):

- **A)** Patient ≥ 18 years of age; AND
- **B)** Cablivi was initiated in the inpatient setting, in combination with plasma exchange therapy; AND
- **C)** Patient is currently receiving at least one immunosuppressive therapy; AND
  Note: Examples include systemic corticosteroids, rituximab (or a rituximab product), cyclosporine, cyclophosphamide, mycophenolate mofetil, hydroxychloroquine, bortezomib.
- **D)** 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
- **E)** The medication is prescribed by or in consultation with a hematologist.

Dosing. Approve the following dosing regimens:

- **A)** Day 1 of treatment with plasma exchange: Two doses of Cablivi (11 mg intravenous [IV] bolus prior to plasma exchange followed by an 11 mg subcutaneous [SC] dose after completion of plasma exchange); AND
- **B)** 11 mg SC injection up to once daily; AND
- **C)** Do not exceed 60 doses following the last plasma exchange session.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cablivi 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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7. Scully M, Hunt BJ, Benjamin S, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *Br J Haematol*. 2012;158:323-335.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Acquired Thrombotic Thrombocytopenic Purpura:** Clarified the dosing schedule for Day 1 of treatment with plasma exchange – one dose of Cablivi prior to plasma exchange followed by one dose after completion of plasma exchange.	02/09/2022
Annual Revision	No criteria changes.	02/22/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Ceprotin Utilization Management Medical 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]

Dosing Information

Dosing is highly individualized. Guidance specific to protein C deficiency is limited. The National Hemophilia Foundation Medical and Scientific Advisory Council (MASAC) provides recommendations regarding doses of clotting factor concentrate in the home (2016).[5] The number of required doses varies greatly and is dependent on the severity of the disorder and the prescribed regimen. Per MASAC guidance, patients on prophylaxis should also have a minimum of one major dose and two minor doses on hand for breakthrough episodes in addition to the prophylactic doses used monthly. The guidance also notes that an adequate supply of clotting factor concentrate is needed to accommodate weekends and holidays. Therefore, maximum doses in this policy allow for prophylactic dosing plus three days of acute episodes or perioperative management per 28 days. Doses exceeding this quantity will be reviewed on a case-by-case basis by a clinician.

Dosing considerations for individual indications are as follows:

- **Protein C Deficiency, Severe:** For routine prophylaxis, the maximum dose is 60 IU/kg once every 12 hours.[1] For acute episodes or perioperative prophylaxis, the prescribing information recommends a loading dose up to 120 IU/kg once, followed by 80 IU/kg every 6 hours for 3 doses, followed by 60 IU/kg every 6 hours thereafter.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Ceprotin. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **Protein C Deficiency, Severe.** Approve for 1 year if the patient meets the following (A, B, C, and D)
   - **A)** The diagnosis of protein C deficiency is confirmed by at least one of the following (i, ii, or iii):
     - **i.** Plasma protein C activity below the lower limit of normal based on the age-specific reference range for the reporting laboratory; OR
     - **ii.** Plasma protein C antigen below the lower limit of normal based on the age-specific reference range for the reporting laboratory; OR
     - **iii.** Genetic testing demonstrating biallelic mutations in the *PROC* gene; AND
   - **B)** 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.
   - **C)** According to the prescriber, patient has a current or prior history of symptoms associated with severe protein C deficiency (e.g., purpura fulminans, thromboembolism); AND
   - **D)** Ceprotin is being prescribed by or in consultation with a hematologist.

   Dosing. Approve up to 4,440 IU/kg intravenously per 28 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ceprotin 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. Ceprotin® intravenous infusion [prescribing information]. Lexington, MA: Baxalta/Shire; August 2021.
2. Protein C Deficiency. National Organization of Rare Disorders. Updated 2016. Available at: https://rarediseases.org/rare-diseases/protein-c-deficiency/. Accessed on November 5, 2023.
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4. Cooper PC, Pavlova A, Moore GW, et al. Recommendations for clinical laboratory testing for protein C deficiency, for the subcommittee on plasma coagulation inhibitors of the ISTH. *J Thromb Haemost*. 2020 Feb;18(2):271-277.
5. MASAC (Medical and Scientific Advisory Council) recommendations regarding doses of clotting factor concentrate used in the home. MASAC Document #242. Adopted on June 7, 2016. Available at: https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations/MASAC-Recommendations-Regarding-Doses-of-Clotting-Factor-Concentrate-in-the-Home. Accessed on November 5, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/02/2022
Annual Revision	No criteria changes.	11/08/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Coagadex Utilization Management Medical 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 Hemophilia Foundation Medical and Scientific Advisory Council (MASAC) has guidelines for the treatment of hemophilia and other bleeding disorders (revised February 2022).[6] Coagadex is recommended in patients who have Factor X deficiency.

Dosing Considerations

Dosing of clotting factor concentrates is highly individualized. MASAC provides recommendations regarding doses of clotting factor concentrate in the home (2016).[7] The number of required doses varies greatly and is dependent on the severity of the disorder and the prescribed regimen. Per MASAC guidance, patients on prophylaxis should also have a minimum of one major dose and two minor doses on hand for breakthrough bleeding in addition to the prophylactic doses used monthly. The guidance also notes that an adequate supply of clotting factor concentrate is needed to accommodate weekends and holidays. Therefore, maximum doses in this policy allow for prophylactic dosing plus three days of acute bleeding or perioperative management per 28 days. Doses exceeding this quantity will be reviewed on a case-by-case basis by a clinician.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage Coagadex. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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, 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 Coagadex is recommended for patients who meet the following criteria:

FDA-Approved Indication

1. **Hereditary Factor X Deficiency.** Approve for 1 year if the agent is prescribed by or in consultation with a hematologist.

   Dosing. Approve up to 600 IU/kg by intravenous infusion no more frequently than once every 28 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Coagadex 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. Coagadex® intravenous infusion [prescribing information]. Durham, NC: BPL; April 2023.
2. 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].
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4. Menegatti M, Peyvandi F. Treatment of rare factor deficiencies other than hemophilia. *Blood*. 2019;133(5):415-424.
5. 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.
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7. National Hemophilia Foundation. MASAC (Medical and Scientific Advisory Council) recommendations regarding doses of clotting factor concentrate in the home (Revised June 7, 2016). MASAC Document #242. Adopted on June 7, 2016. Available at: https://www.hemophilia.org/sites/default/files/document/files/242.pdf. Accessed on November 5, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	10/19/2022
Annual Revision	No criteria changes.	11/08/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Corifact Utilization Management Medical 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.

Dosing Considerations

Dosing of clotting factor concentrates is highly individualized. MASAC provides recommendations regarding doses of clotting factor concentrate in the home (2016).[5] The number of required doses varies greatly and is dependent on the severity of the disorder and the prescribed regimen. Per MASAC guidance, patients on prophylaxis should also have a minimum of one major dose and two minor doses on hand for breakthrough bleeding in addition to the prophylactic doses used monthly. The guidance also notes that an adequate supply of clotting factor concentrate is needed to accommodate weekends and holidays. Therefore, maximum doses in this policy allow for prophylactic dosing plus three days of acute bleeding or perioperative management per 28 days. Doses exceeding this quantity will be reviewed on a case-by-case basis by a clinician.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage Corifact. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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, 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 Corifact is recommended for patients who meet the following criteria:

FDA-Approved Indication

1. **Congenital Factor XIII Deficiency.** Approve for 1 year if the agent is prescribed by or in consultation with a hematologist.

   Dosing. Approve up to 160 IU/kg by intravenous infusion no more frequently than once every 28 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Corifact 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. Corifact® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; September 2020.
2. Menegatti M, Peyvandi F. Treatment of rare factor deficiencies other than hemophilia. *Blood*. 2019;133(5):415-424.
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4. 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.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	10/19/2022
Annual Revision	No criteria changes.	11/08/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Enjaymo Utilization Management Medical Policy
- Enjaymo® (sutimlimab-jome intravenous infusion – Bioverativ/Sanofi)

REVIEW DATE: 01/11/2023

OVERVIEW

Enjaymo, a classical complement inhibitor, is indicated for the treatment of hemolysis in adults with **cold agglutinin disease**.[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] 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.[6]

Dosing Information

Dosing is weight-based and is provided for patients weighing ≥ 39 kg.[1] For a patient weighing 39 to < 75 kg, the recommended dose is 6,500 mg. For a patient weighing ≥ 75 kg, the dose is 7,500 mg. For all patients, the initial dosing frequency is once weekly for 2 weeks, with administration once every 2 weeks (Q2W) thereafter. However, if the interval between doses exceeds 17 days, Enjaymo should be administered once weekly for 2 weeks, returning to Q2W administration thereafter.

Guidelines

An international consensus guideline for autoimmune hemolytic anemias was published in 2020.[7] 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 medical benefit coverage of Enjaymo. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **Cold Agglutinin Disease.** Approve for 1 year 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 weighs ≥ 39 kg; AND
   - **C)** Patient has a history 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.

Dosing: Approve the following dosing regimens (A or B):

A) Patient weighs ≥ 75 kg: Approve 7,500 mg intravenously not more frequently than once weekly.

B) Patient weighs < 75 kg: Approve 6,500 mg intravenously not more frequently than once weekly.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Enjaymo 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. Enjaymo™ intravenous infusion [prescribing information]. Waltham, MA: Bioverativ/Sanofi; February 2022.
2. Berentsen S, Röth A, Randen U, et al. Cold agglutinin disease: current challenges and future prospects. *J Blood Med*. 2019;10:93-103.
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4. Swiecicki PL, Hegerova LT, Gertz MA. Cold agglutinin disease. *Blood*. 2013;122(7):1114-1121.
5. Röth A, Barcellini W, D'Sa S, et al. Sutimlimab in cold agglutinin disease. *N Engl J Med*. 2021;384(14):1323-1334.
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7. 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	02/16/2022
Early Annual Revision	No criteria changes.	01/11/2023
Update	02/20/2023: No criteria changes. Updated the wording of the indication.	NA

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Fibrinogen Products Utilization Management Medical 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.

Dosing Information

Dosing is highly individualized. Guidance specific to congenital fibrinogen deficiency is limited. The National Hemophilia Foundation Medical and Scientific Advisory Council (MASAC) provides recommendations regarding doses of clotting factor concentrate in the home (2016).[9] The number of required doses varies greatly and is dependent on the severity of the disorder and the prescribed regimen. Per MASAC guidance, patients on prophylaxis should also have a minimum of one major dose and two minor doses on hand for breakthrough episodes in addition to the prophylactic doses used monthly. The guidance also notes that an adequate supply of clotting factor concentrate is needed to accommodate weekends and holidays. Therefore, maximum doses in this policy allow for prophylactic dosing plus three days of acute episodes or perioperative management per 28 days. Doses exceeding this quantity will be reviewed on a case-by-case basis by a clinician.

Dosing considerations for individual indications are as follows:

- **Congenital Fibrinogen Deficiency, Including Afibrinogenemia and Hypofibrinogenemia:** Doses of Fibryga and RiaSTAP are individualized based on patient-specific characteristics (e.g., extent of bleeding, clinical condition, laboratory values).[1,2] Treatment with fibrinogen products is repeated as needed to maintain target levels. Based on the product half-lives of approximately three days[1,2], it is not anticipated that dosing more frequent than once daily would typically be needed. On-demand doses up to 100 mg/kg are supported.[7] Prophylactic dosing is not well established; doses up to 100 mg/kg and intervals as frequent as once weekly have been reported.[7]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of fibrinogen products (Fibryga, RiaSTAP). Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **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.

   Dosing. Approve up to 700 mg/kg intravenously per 28 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Fibryga and RiaSTAP is not recommended in the following situations:

1. **Concomitant Use of Fibryga and RiaSTAP.** There are no data to support concomitant use of these products.

2. **Dysfibrinogenemia.** In dysfibrinogenemia, patients have adequate levels of fibrinogen but dysfunctional clotting.[3,4] Fibryga and RiaSTAP are not indicated for dysfibrinogenemia.[1,2]

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

1. RiaSTAP® intravenous injection [prescribing information]. Kankakee, IL: CSL Behring; June 2021.
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9. MASAC (Medical and Scientific Advisory Council) recommendations regarding doses of clotting factor concentrate in the home. MASAC Document #242. Adopted on June 7, 2016. Available at: https://www.hemophilia.org/sites/default/files/document/files/242.pdf. Accessed on November 5, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/02/2022
Annual Revision	No criteria changes.	11/08/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Gene Therapy – Zynteglo Utilization Management Medical 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 benefit coverage of Zynteglo. Approval is recommended for those who meet the **Criteria** and **Dosing** 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 administered 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 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 Zynteglo is recommended in those who meet the following criteria:

FDA-Approved Indication

1. Beta Thalassemia. Approve for 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 $\beta^0/\beta^{+(\text{IVS-I-110})}$ and $\beta^{+(\text{IVS-I-110})}/\beta^{+(\text{IVS-I-110})}$.

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 history 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.

Dosing. The recommended dose of Zynteglo is a single intravenous infusion which contains a minimum of 5.0 x 10^6 CD34+ cells/kg of body weight.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zynteglo is not recommended in the following situations:

1. **Concurrent Use with Reblozyl** (luspatercept-aamt subcutaneous injection). Reblozyl was not utilized with Zynteglo in the pivotal trials.

2. **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.

3. **Prior Receipt of Gene Therapy**. Prior receipt of gene therapy was a reason for patient exclusion in the two pivotal trials.

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. Zynteglo™ intravenous infusion [prescribing information]. Somerville, MA: Bluebird Bio; August 2022.
2. Taher AT, Musallam KM, Cappellini MD, et al. β-thalassemias. *N Engl J Med*. 2021;384;727-743.
3. Locatelli F, Thompson AA, Kwiatkowski JL, et al. Betibeglogene autotemcel gene therapy for non-β^0/β^0 genotype β-thalassemia. *N Engl J Med*. 2022;386:417-427.
4. Farmakis D, Porter J, Taher A, et al, for the 2021 TIF Guidelines Taskforce. 2021 Thalassaemia International Federation guidelines for the management of transfusion-dependent thalassemia. *Hemasphere*. 2022;6:8(e732).

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/28/2022
Selected Revision	The phase "Gene Therapy" was added to the header. In addition, the following change was made: **Beta Thalassemia:** Criteria changed from "Patient has a recent white blood cell count ≥ 3 x 10^9/L [documentation required]"; OR "Patient has a recent platelet count ≥ 100 x 10^9/L [documentation required]" to requiring both criterion be met.	10/19/2022
Annual Revision	In the Policy Statement [attestation required by physician] was removed from this policy. It was added that for certain criteria, verification is required as noted by [verification in claims history required]. In addition, the following changes were made: 1. **Beta Thalassemia:** The phrase "as determined by the prescribing physician" was removed from the requirement regarding that the patient is without an active infection (bacterial, viral, fungal, or parasitic). The phrase "plans to" was changed to "will" to be more directive in the requirement that the patient undergoes mobilization, apheresis, and myeloablative conditioning. Regarding the requirement that Mozobil will be utilized for mobilization, this was changed to the more broad term "hematopoietic stem cell mobilizer" and Mozobil was added to the Note stating that it is an example of a hematopoietic stem cell mobilizer. In the requirement that use of iron chelators will be avoided for 6 months after infusion of Zynteglo, the [attestation required by physician] was removed. The word "recent" was replaced with the phrase "within 30 days before intended receipt of Zynteglo" regarding meeting thresholds for white blood cell count and platelet count. Regarding the requirement that the patient does not have evidence of severe iron overload, the [attestation required by physician] was removed. It was added that the patient has not received Zynteglo in the past, with [verification in claims history required]. Dosing was added in an additional section with the other standard requirements for alignment with similar policies; dosing requirements were always present with Zynteglo for this policy. 2. **Conditions Not Recommended for Approval:** The [attestation required by physician] was removed from the exclusion regarding prior hematopoietic stem cell transplantation. A Note was added that the prescribing physician must confirm that the patient has not received a prior hematopoietic stem cell transplantation.	11/01/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Ryplazim Utilization Management Medical Policy
- Ryplazim® (plasminogen, human-tvmh intravenous infusion – Prometic/Kedrion)

REVIEW DATE: 01/04/2023

OVERVIEW

Ryplazim, a plasma-derived human plasminogen, is indicated for the treatment of patients with **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). 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.

Dosing Information

Ryplazim dosing frequency is adjusted based on trough plasminogen activity level; the most frequent recommended dosing interval is once every other day. It is recommended to continue dosing for 12 weeks while treating active lesions and then assess for clinical response. If lesions do not resolve by 12 weeks, or if there are new or recurrent lesions, dosing frequency can be escalated (to a maximum of every other day) while assessing clinical improvement until lesion resolution or until the lesions stabilize without further worsening. If desired clinical change does not occur by 12 weeks, an additional trough plasminogen activity level should be obtained. If the trough level is ≥ 10% (absolute change in plasminogen activity) above baseline, surgical removal of the lesions should be considered in addition to plasminogen treatment. If the trough level is < 10% baseline (in combination with no clinical efficacy), consider discontinuing plasminogen treatment due to the possibility of neutralizing antibodies.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Ryplazim. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **Plasminogen Deficiency Type 1 (Hypoplasminogenemia).** 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 criteria (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 criteria (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.

   Dosing. Approve a dose of 6.6 mg/kg body weight intravenously, not more frequency than once every other day.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ryplazim 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. Ryplazim® intravenous infusion [prescribing information]. Laval, Quebec, Canada: Prometic; November 2021.
2. Shapiro AD, Menegatti M, Palla R, et al. An international registry of patients with plasminogen deficiency (HISTORY). *Haematologica*. 2020 Mar;105(3):554-561.
3. Schuster V, Hügle B, Tefs K. Plasminogen deficiency. *J Thromb Haemost*. 2007 Dec;5(12):2315-22.
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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/12/2022
Early Annual Revision	No criteria changes.	01/04/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Tretten Utilization Management Medical 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 (MASAC) 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.

Dosing Considerations

Dosing of clotting factor concentrates is highly individualized. MASAC provides recommendations regarding doses of clotting factor concentrate in the home (2016).[5] The number of required doses varies greatly and is dependent on the severity of the disorder and the prescribed regimen. Per MASAC guidance, patients on prophylaxis should also have a minimum of one major dose and two minor doses on hand for breakthrough bleeding in addition to the prophylactic doses used monthly. The guidance also notes that an adequate supply of clotting factor concentrate is needed to accommodate weekends and holidays. Therefore, maximum doses in this policy allow for prophylactic dosing plus three days of acute bleeding or perioperative management per 28 days. Doses exceeding this quantity will be reviewed on a case-by-case basis by a clinician.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage Tretten. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director

or Pharmacist). 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, 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 Tretten is recommended for patients who meet the following criteria:

FDA-Approved Indication

1. **Congenital Factor XIII A-Subunit Deficiency.** Approve for 1 year if the agent is prescribed by or in consultation with a hematologist.

   Dosing. Approve up to 140 IU/kg intravenously no more frequently than once every 28 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tretten is not recommended in the following situations:

1. **Congenital Factor XIII B-Subunit Deficiency.** Tretten will not work in patients who only lack Factor XIII-B subunit.[1,2]

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. Tretten® intravenous infusion [prescribing information]. Plainsboro, NJ: Novo Nordisk; June 2020.
2. Menegatti M, Peyvandi F. Treatment of rare factor deficiencies other than hemophilia. *Blood*. 2019;133(5):415-424.
3. 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.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	10/19/2022
Annual Revision	No criteria changes.	11/08/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Vonvendi Management Medical 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.[3-6] 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 (MASAC) 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.

Dosing Considerations

Dosing of clotting factor concentrates is highly individualized. MASAC provides recommendations regarding doses of clotting factor concentrate in the home (2016).[7] The number of required doses varies greatly and is dependent on the severity of the disorder and the prescribed regimen. Per MASAC guidance, patients on prophylaxis should also have a minimum of one major dose and two minor doses on hand for breakthrough bleeding in addition to the prophylactic doses used monthly. The guidance also notes that an adequate supply of clotting factor concentrate is needed to accommodate weekends and holidays. Therefore, maximum doses in this policy allow for prophylactic dosing plus three days of acute bleeding or perioperative management per 28 days. Doses exceeding this quantity will be reviewed on a case-by-case basis by a clinician.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage Vonvendi. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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, 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 Vonvendi is recommended for patients who meet the following criteria:

FDA-Approved Indication

1. Von Willebrand Disease. Approve for 1 year if the agent is prescribed by or in consultation with a hematologist.

Dosing. Approve the following dosing regimens (A, B, and/or C):

A) On demand treatment and control of bleeding episodes: approve up to 900 IU/kg intravenously no more frequently than once every 28 days; AND/OR
B) Perioperative management: approve up to 900 IU/kg intravenously no more frequently than once every 28 days; AND/OR
C) Routine prophylaxis: approve up to 60 IU/kg intravenously no more frequently than twice weekly.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vonvendi 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. Vonvendi® intravenous infusion [prescribing information]. Lexington, MA: Baxalta; March 2023.
2. Gill JC, Castaman G, Windyga J, et al. Hemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease. *Blood*. 2015;126(17):2038-2046.
3. Franchini M, Mannucci PM. Von Willebrand factor (Vonvendi®): the first recombinant product licensed for the treatment of von Willebrand disease. *Expert Rev Hematol*. 2016;9(9):825-830.
4. 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.
5. Srivastava A, Santagostino E, Dougall A, et al, on behalf of the WFH guidelines for the management of hemophilia panelists and coauthors. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia*. 2020;26 Suppl 6:1-158.
6. Connell NT, Flood VH, Brignardello-Petersen R, et al. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand Disease. *Blood Adv*. 2021;5(1):301-325.
7. National Hemophilia Foundation. MASAC (Medical and Scientific Advisory Council) recommendations regarding doses of clotting factor concentrate in the home (Revised June 7, 2016). MASAC Document #242. Adopted on September 3, 2020. Available at: https://www.hemophilia.org/sites/default/files/document/files/242.pdf. Accessed on November 5, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Selected Revision	**Von Willebrand Disease:** Added dosing for routine prophylaxis to approve up to 60 IU/kg intravenously no more frequently than twice weekly.	02/16/2022
Annual Revision	No criteria changes.	10/19/2022
Annual Revision	No criteria changes.	11/08/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hemophilia – Eptacog Products – Sevenfact Utilization Management Medical 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]

Dosing Information

Sevenfact is only indicated in the acute treatment setting for treatment of bleeding events. In the prescribing information, it is noted that maximum tolerated doses have not been determined for Sevenfact, and cumulative daily doses greater than 900 mcg/kg, which may be associated with greater risk of thromboembolic complications, have not been studied.[1] The National Hemophilia Foundation Medical and Scientific Advisory Council (MASAC) provides recommendations regarding doses of clotting factor concentrate in the home (2016).[4] Per MASAC guidance, patients on prophylaxis should also have a minimum of one major dose and two minor doses on hand for breakthrough episodes. The guidance also notes that an adequate supply of clotting factor concentrate is needed to accommodate weekends and holidays. Therefore, maximum doses in this policy allow for three days of acute bleeding per 28 days. Doses exceeding this quantity will be reviewed on a case-by-case basis by a clinician.

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**.[5] 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 not 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 medical benefit coverage of Sevenfact. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

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1. **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.

   Dosing. Approve up to 2,700 mcg/kg intravenously per 28 days.

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2. **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 history 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.

Dosing. Approve up to 2,700 mcg/kg intravenously per 28 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sevenfact 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. Sevenfact® intravenous infusion [prescribing information]. Les Ulis, France/Louisville, KY: LFB S.A./Hema Biologics; November 2022.
2. Meeks SL, Leissinger CA. The evolution of factor VIIa in the treatment of bleeding in haemophilia with inhibitors. *Haemophilia*. 2019;25(6):911-918.
3. Srivastava A, Santagostino E, Dougall A, et al; WFH Guidelines for the Management of Hemophilia panelists and co-authors. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia*. 2020 Aug;26 Suppl 6:1-158.
4. MASAC (Medical and Scientific Advisory Council) recommendations regarding doses of clotting factor concentrate in the home. MASAC Document #242. Adopted on June 7, 2016. Available at: https://www.hemophilia.org/sites/default/files/document/files/242.pdf. Accessed on November 5, 2023.
5. 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/02/2022
Annual Revision	No criteria changes.	11/08/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hemophilia – Factor IX Products Utilization Management Medical 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 Standard Half-Life 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 medical benefit coverage of the following Factor IX products: Alprolix, Idelvion, Rebinyn, BeneFIX, Ixinity, Rixubis, AlphaNine, Mononine, and Profilnine. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the criteria and dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

Coverage of the following Factor IX products is recommended for patients who meet criteria: Alprolix, Idelvion, Rebinyn, BeneFIX, Ixinity, Rixubis, AlphaNine, Mononine, and Profilnine.

I. Coverage of Alprolix, Idelvion, Rebinyn, BeneFIX, Ixinity, and Rixubis 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.

Dosing. Approve one of the following dosing regimens (A or B):

A) For Alprolix, Idelvion, and Rebinyn approve the following dosing regimens (i, ii, and/or iii):

- **i.** Routine prophylaxis: approve up to 100 IU per kg intravenously at an interval no more frequently than once weekly; AND/OR;
- **ii.** On-demand treatment and control of bleeding episodes: approve up to 100 IU per kg intravenously no more frequently than once every 6 hours for up to 10 days per episode; AND/OR
- **iii.** Perioperative management: approve up to 100 IU per kg intravenously no more frequently than once every 24 hours for up to 10 days per procedure; OR

B) For BeneFIX, Ixinity, and Rixubis approve the following dosing regimens (i, ii, iii, and/or iv):
- **i.** Routine prophylaxis: approve up to 100 IU per kg intravenously no more frequently than twice weekly; AND/OR
- **ii.** On-demand treatment and control of bleeding episodes: approve up to 100 IU per kg intravenously no more frequently than once every 12 hours for up to 10 days per episode; AND/OR
- **iii.** Perioperative management: approve up to 100 IU per kg intravenously no more frequently than once every 8 hours for up to 10 days per procedure; AND/OR
- **iv.** Immune tolerance therapy (also known as immune tolerance induction): approve up to 200 IU per kg intravenously no more frequently than once daily.

II. Coverage of AlphaNine SD, Mononine, and Profilnine is recommended for patients who meet the following criteria:

FDA-Approved Indication

1. Hemophilia B. Approve AlphaNine SD, Mononine, and Profilnine for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

Dosing. Approve the following dosing regimens:
A) Routine prophylaxis: approve up to 50 IU per kg intravenously no more frequently than twice weekly; AND/OR
B) On-demand treatment of and control of bleeding episodes and perioperative management: approve up to 100 IU per kg intravenously no more frequently than twice daily for up to 10 days; AND/OR
C) Immune tolerance therapy (also known as immune tolerance induction): approve up to 200 IU per kg intravenously no more frequently than once daily.

III. Coverage of Profilnine is also recommended for patients who meet the following criteria:

Other Uses with Supportive Evidence

1. Factor II Deficiency. Approve Profilnine for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

Dosing. Limited dosing is available. Recommended dosing in hemophilia B (an FDA-approved use) is cited below.
A) Routine prophylaxis: approve up to 50 IU per kg intravenously no more frequently than twice weekly; AND/OR
B) On-demand treatment of and control of bleeding episodes and perioperative management: approve up to 100 IU per kg intravenously no more frequently than twice daily for up to 10 days.

2. Factor X Deficiency. Approve Profilnine for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

Dosing. Limited dosing is available. Recommended dosing in hemophilia B (an FDA-approved use) is cited below.

A) Routine prophylaxis: approve up to 50 IU per kg intravenously no more frequently than twice weekly; AND/OR

B) On-demand treatment of and control of bleeding episodes and perioperative management: approve up to 100 IU per kg intravenously no more frequently than twice daily for up to 10 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of the cited Factor IX products are 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. 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	03/09/2022
Annual Revision	No criteria changes.	03/22/2022

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hemophilia – Factor VIII Products Utilization Management Medical Policy

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 for intravenous infusion – Octapharma)

REVIEW DATE: 03/22/2023

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] 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 involve 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 medical 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. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the criteria and dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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1. Hemophilia A. Approve the requested agent for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

Dosing. Approve one of the following dosing regimens (A or B):

A) For Adynovate, Eloctate, Esperoct, and Jivi approve the following dosing regimens (i, ii, and/or iii):
- **i.** Routine prophylaxis: approve up to 100 IU per kg intravenously no more frequently than twice weekly; AND/OR
- **ii.** On-demand treatment and control of bleeding episodes: approve up to 65 IU per kg intravenously no more frequently than once every 8 hours for up to 10 days per episode; AND/OR
- **iii.** Perioperative management: approve up to 65 IU per kg intravenously no more frequently than once every 6 hours for up to 10 days per procedure; OR

B) For Advate, Afstyla, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, and Xyntha approve the following dosing regimens (i, ii, iii, and/or iv):
- **i.** Routine prophylaxis: approve up to 60 IU per kg intravenously no more frequently than every other day (three or four times weekly); AND/OR
- **ii.** On-demand treatment and control of bleeding episodes: approve up to 50 IU per kg intravenously no more frequently than once every 6 hours for up to 10 days per episode; AND/OR
- **iii.** Perioperative management: approve up to 60 IU per kg intravenously no more frequently than once every 6 hours for up to 10 days per procedure; AND/OR
- **iv.** Immune tolerance therapy (also known as immune tolerance induction): approve up to 200 IU per kg intravenously no more frequently than once daily.

II. Coverage of Hemofil M and Koate is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. Hemophilia A. Approve for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

Dosing. Approve the following dosing regimens:

A) Routine prophylaxis: approve up to 50 IU per kg intravenously no more frequently than every other day (three or four times weekly); AND/OR

B) On-demand treatment and control of bleeding episodes and perioperative management: approve up to 50 IU per kg intravenously no more frequently than once every 6 hours for up to 10 days per episode or procedure; AND/OR

C) Immune tolerance therapy (also known as immune tolerance induction): approve up to 200 IU per kg intravenously no more frequently than once daily.

III. Coverage of Alphanate, Humate-P, and Wilate is recommended in those who meet the following criteria:

FDA-Approved Indications

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1. Hemophilia A. Approve for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

Dosing. Approve the following dosing regimens:

A) Routine prophylaxis: approve up to 50 IU per kg intravenously no more frequently than every other day (three or four times weekly); AND/OR

B) On-demand treatment and control of bleeding episodes and perioperative management: approve up to 50 IU per kg intravenously no more frequently than once every 6 hours for up to 10 days per episode or procedure; AND/OR

C) Immune tolerance therapy (also known as immune tolerance induction): approve up to 200 IU per kg intravenously no more frequently than once daily.

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2. Von Willebrand Disease. Approve for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

Dosing. On-demand treatment and control of bleeding episodes and perioperative management: approve up to 80 IU VWF:RCo per kg intravenously no more frequently than once every 8 hours for up to 10 days per episodes or procedure.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of the cited Factor VIII 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

1. Adynovate® intravenous infusion [prescribing information]. Lexington, MA: Baxalta; June 2021.
2. Eloctate® intravenous infusion [prescribing information]. Waltham, MA: Bioverativ; December 2020.
3. Jivi® intravenous infusion [prescribing information]. Whippany, NJ: Bayer; August 2018.
4. Esperoct® intravenous infusion [prescribing information]. Plainsboro, NJ: Novo Nordisk; August 2022.
5. Advate® intravenous infusion [prescribing information]. Westlake Village, CA: Baxalta/Shire; December 2018.
6. Kovaltry® intravenous infusion [prescribing information]. Whippany, NJ: Bayer; December 2022.
7. Afstyla® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; April 2021.
8. Kogenate® FS lyophilized powder for reconstitution for intravenous infusion [prescribing information]. Whippany, NJ: Bayer; December 2019.
9. Novoeight® intravenous infusion [prescribing information]. Plainsboro, NJ: Novo Nordisk; July 2020.
10. Nuwiq® intravenous infusion [prescribing information]. Paramus, NJ: Octapharma; June 2021.
11. Recombinate™ intravenous infusion [prescribing information]. Lexington, MA: Baxalta; June 2021.
12. Xyntha® intravenous infusion [prescribing information]. Philadelphia, PA: Wyeth/Pfizer; July 2022.
13. Xyntha® Solofuse™ intravenous infusion [prescribing information]. Philadelphia, PA: Wyeth/Pfizer; July 2022.
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16. Humate-P® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; June 2020.

17. Koāte® intravenous infusion [prescribing information]. Fort Lee, NJ and Research Triangle Park, NC: Kedrion and Grifols; June 2018.
18. Wilate® intravenous infusion [prescribing information]. Hoboken, NJ: Octapharma; September 2019.
19. Altuviiio™ intravenous infusion [prescribing information]. Waltham, MA: Bioverativ/Sanofi; February 2023.
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25. Neff AT, Sidonio RF. Management of VWD. *Hematology Am Soc Hematol Educ Program*. 2014;(1):536-541.
26. 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.
27. Favaloro EJ, Bodo I, Israels SJ, Brown SA. Von Willebrand disease and platelet disorders. *Hemophilia*. 2014;20(Suppl 4):59-64.
28. 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	03/09/2022
Annual Revision	Removed Helixate/Helixate FS and Monoclate P from the policy as both products are obsolete.	03/22/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hemophilia – FEIBA Utilization Management Medical 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]

Dosing Information

Dosing of clotting factor concentrates is highly individualized. MASAC provides recommendations regarding doses of clotting factor concentrate in the home (2016).[4] The number of required doses varies greatly and is dependent on the severity of the disorder and the prescribed regimen. Per MASAC guidance, patients on prophylaxis should also have a minimum of one major dose and two minor doses on hand for breakthrough episodes in addition to the prophylactic doses used monthly. The guidance also notes that an adequate supply of clotting factor concentrate is needed to accommodate weekends and holidays. Therefore, maximum doses in this policy allow for prophylactic dosing plus three days of acute episodes or perioperative management per 28 days. Doses exceeding this quantity will be reviewed on a case-by-case basis by a clinician.

Dosing considerations for individual indications are as follows:

- **Hemophilia A with Inhibitors** and **Hemophilia B with Inhibitors:** For routine prophylaxis, a dose of 85 units/kg every other day is recommended.[1] Dosing for acute episodes and perioperative management can range up to 100 units/kg every 6 hours (400 units/kg daily dose).

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of FEIBA. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the criteria and dosing. Requests for doses outside of the established dosing

documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 this 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 FEIBA is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **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.

   Dosing. Approve up to a maximum of 2,390 units/kg intravenously per 28 days.

2. **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 history 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.

   Dosing. Approve up to a maximum of 2,390 units/kg intravenously per 28 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of FEIBA 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. FEIBA® intravenous infusion [prescribing information]. Lexington, MA: Baxalta/Takeda; March 2023.
2. 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.
3. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia*. 2020;26 Suppl 6:1-158.
4. MASAC (Medical and Scientific Advisory Council) recommendations regarding doses of clotting factor concentrate in the home. MASAC Document #242. Adopted on June 7, 2016. Available at: https://www.hemophilia.org/sites/default/files/document/files/242.pdf. Accessed on November 8, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/02/2022
Annual Revision	No criteria changes.	11/08/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hemophilia – Gene Therapy – Hemgenix Utilization Management Medical 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 ≤ 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.

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 Hemgenix is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **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 history 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 2×10^{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.

Dosing. The recommended dose of Hemgenix is a single one time (per lifetime) intravenous infusion of 2×10^{13} genome copies based on current body weight in kg (within the past 30 days).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Hemgenix 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.

Table 1. Hemgenix Multi-Vial Kits.[1]

Total Number of Vials per Kit	Patient Body Weight	Total Volume per Kit	NDC Number
10	46 to 50 kg	100	0053-0100-10
11	51 to 55 kg	110	0053-0110-11
12	56 to 60 kg	120	0053-0120-12
13	61 to 65 kg	130	0053-0130-13
14	66 to 70 kg	140	0053-0140-14
15	71 to 75 kg	150	0053-0150-15
16	76 to 80 kg	160	0053-0160-16
17	81 to 85 kg	170	0053-0170-17
18	86 to 90 kg	180	0053-0180-18
19	91 to 95 kg	190	0053-0190-19
20	96 to 100 kg	200	0053-0200-20
21	101 to 105 kg	210	0053-0210-21
22	106 to 110 kg	220	0053-0220-22
23	111 to 115 kg	230	0053-0230-23
24	116 to 120 kg	240	0053-0240-24
25	121 to 125 kg	250	0053-0250-25
26	126 to 130 kg	260	0053-0260-26
27	131 to 135 kg	270	0053-0270-27
28	136 to 140 kg	280	0053-0280-28
29	141 to 145 kg	290	0053-0290-29
30	146 to 150 kg	300	0053-0300-30
31	151 to 155 kg	310	0053-0310-31
32	156 to 160 kg	320	0053-0320-32
33	161 to 165 kg	330	0053-0330-33
34	166 to 170 kg	340	0053-0340-34
35	171 to 175 kg	350	0053-0350-35
36	176 to 180 kg	360	0053-0360-36
37	181 to 185 kg	370	0053-0370-37
38	186 to 190 kg	380	0053-0380-38
39	191 to 195 kg	390	0053-0390-39
40	196 to 200 kg	400	0053-0400-40
41	201 to 205 kg	410	0053-0410-41
42	206 to 210 kg	420	0053-0420-42
43	211 to 215 kg	430	0053-0430-43
44	216 to 220 kg	440	0053-0440-44
45	221 to 225 kg	450	0053-0450-45
46	226 to 230 kg	460	0053-0460-46
47	231 to 235 kg	470	0053-0470-47
48	236 to 240 kg	480	0053-0480-48

NDC – National Drug Code.

REFERENCES

1. Hemgenix® intravenous infusion [prescribing information]. King of Prussia, PA; Kankakee, IL; and Lexington, MA: CSL Behring and uniQure; November 2022.
2. National Hemophilia Foundation. Hemophilia B. An overview of symptoms, genetics, and treatments to help you understand hemophilia B. Available at: https://www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-b. Accessed on January 11, 2023.
3. Sidonio RF, Malec L. Hemophilia (Factor IX deficiency). *Hematol Oncol Clin N Am*. 2021;35:1143-1155.
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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/11/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hemophilia – Gene Therapy – Roctavian Utilization Management Medical 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.

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 Roctavian is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **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
     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

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

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

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.

Dosing. The recommended dose of Roctavian is a single one time (per lifetime) intravenous infusion of 6 x 10^{13} vector genomes per kg based on current body weight in kg (within the past 30 days).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Roctavian 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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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/16/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hemophilia – Hemlibra Utilization Management Medical 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 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 medical benefit coverage of Hemlibra. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed for the duration noted below if the patient continues to meet the criteria and dosing for the indication provided. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). Because of the specialized skills required for evaluation and diagnosis of patients treated with Hemlibra as well as the monitoring required for adverse events and long-term efficacy, approval requires Hemlibra to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

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1. Hemophilia A with Factor VIII Inhibitors. Approve for 1 year if the patient meets the following (A or B):

A) 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

B) 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 agent 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 product 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 bleeds.

Dosing. Approve the following dosing regimens (A and B):

A) Loading dose is 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks; AND

B) The patient is receiving one of the following maintenance doses (i, ii, or iii):
- **i.** 1.5 mg/kg by subcutaneous injection once every week, OR
- **ii.** 3 mg/kg SC by subcutaneous injection once every 2 weeks; OR
- **iii.** 6 mg/kg SC by subcutaneous injection once every 4 weeks.

2. 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.

Dosing. Approve the following dosing regimens (A and B):

A) Loading dose is 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks; AND

B) Patient is receiving one of the following maintenance doses (i, ii, or iii):

i. 1.5 mg/kg by subcutaneous injection once every week, OR

ii. 3 mg/kg by subcutaneous injection once every 2 weeks; OR

iii. 6 mg/kg by subcutaneous injection once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Hemlibra 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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	05/18/2022
Annual Revision	No criteria changes.	05/24/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hepatology – Givlaari Utilization Management Medical 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 medical benefit coverage of Givlaari. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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1. 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 history 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.

Dosing. Approve 2.5 mg/kg administered by subcutaneous injection given no more frequently than once every 30 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Givlaari 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. Givlaari™ intravenous infusion [prescribing information]. Cambridge, MA: Alnylam; February 2023.
2. Porphyria. U.S. National Library of Medicine; National Institutes of Health; Department of Health and Human Services. Available at: https://ghr.nlm.nih.gov/condition/porphyria. Accessed on October 10, 2023.
3. Wang B, Rudnick S, Cengia B, et al. Acute hepatic porphyrias: review and recent progress. *Hepatol Commun.* 2018;3(2):193-206.
4. Bissell DM, Wang B. Acute hepatic porphyria. *J Clin Transl Hepat*. 2015;3(1):17-26.
5. Balwani M, Wang B, Anderson K, et al. Acute hepatic porphyrias: recommendations for evaluation and long term management. *Hepatology*. 2017;66(4):1314-1322.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	10/19/2022
Annual Revision	No criteria changes.	10/18/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hepatology – Panhematin Utilization Management Medical Policy
- Panhematin® (hemin intravenous infusion – Recordati Rare Diseases)

REVIEW DATE: 10/18/2023

OVERVIEW

Panhematin, an enzyme inhibitor derived from processed red blood cells, is indicated for the **amelioration of recurrent attacks of acute intermittent porphyria** (AIP) temporally related to the menstrual cycle in susceptible women, after initial carbohydrate therapy is known or suspected to be inadequate.[1]

Safety and effectiveness in patients < 16 years of age have not been established.[1]

Disease Overview

Porphyria is a group of metabolic disorders caused by abnormalities in the chemical steps that lead to the production of heme.[2] Heme is necessary for the transport of oxygen to cells in the body. If synthesis of heme is hindered, an accumulation of porphyrins or porphyrin precursors (intermediate chemicals) accumulates in the cells, resulting in oxygen depletion. Acute hepatic porphyrias (AHPs) are a subgroup of porphyrias in which the enzyme deficiency occurs within the liver.[3] AHPs include 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, along with elevated urinary aminolevulinic acid and porphobilinogen. Hospitalization is often required for acute attacks. Although most symptomatic patients with AHP have complete resolution of their symptoms between attacks, those with numerous recurrences may develop chronic pain. Due to the high prevalence of chronic kidney disease, serum creatinine and estimated glomerular filtration rate should be monitored annually for all symptomatic patients.

Dosing Information

The recommended dose of Panhematin is 1 to 4 mg/kg/day administered by intravenous infusion for 3 to 14 days based on the clinical signs.[1] The standard dose in clinical practice is 3 to 4 mg/kg/day. Do not exceed 6 mg/kg in any 24 hour period.

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) 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.

Safety

Panhematin is derived from human blood; therefore, there is a potential risk of the transmission of infectious agents (e.g., viruses) that may cause disease.[1] Because increased levels of iron and serum ferritin have been reported in post-marketing experience with Panhematin, providers should monitor iron and serum ferritin in patients receiving multiple doses.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Panhematin. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Panhematin as well as the monitoring required for adverse events and long-term efficacy, approval requires Panhematin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indication

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1. Acute Intermittent Porphyria. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

- **A)** Patient is ≥ 16 years of age; AND
- **B)** Diagnosis of acute intermittent porphyria was confirmed by both of the following (i and ii):
  - **i.** Patient demonstrated clinical features associated with acute intermittent 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)** Acute intermittent porphyria is related to the menstrual cycle; AND
- **D)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, or a physician who specializes in acute intermittent porphyria.

Dosing. Approve up to 6 mg/kg administered by intravenous infusion once daily given no more frequently than 14 days per 30 days.

Other Uses with Supportive Evidence

2. Acute Hepatic Porphyria. Approve for 1 year if the patient meets all of the following (A, B, and C):
- **A)** Patient is ≥ 16 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)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, or a physician who specializes in acute hepatic porphyria.

Dosing. Approve up to 6 mg/kg given by intravenous infusion once daily no more frequently than 14 days per 30 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Panhematin 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. Panhematin® intravenous infusion [prescribing information]. Lebanon, NJ: Recordati Rare Diseases; May 2020.
2. Porphyria. U.S. National Library of Medicine; National Institutes of Health; Department of Health and Human Services. Available at: https://ghr.nlm.nih.gov/condition/porphyria. Accessed on October 10, 2023.
3. Wang B, Rudnick S, Cengia B, et al. Acute hepatic porphyrias: review and recent progress. *Hepatol Commun.* 2018;3(2):193-206.
4. Bissell DM, Wang B. Acute hepatic porphyria. *J Clin Transl Hepat*. 2015;3(1):17-26.
5. Balwani M, Wang B, Anderson K, et al. Acute hepatic porphyrias: recommendations for evaluation and long term management. *Hepatology*. 2017;66(4):1314-1322.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	No criteria changes	10/19/2022
Annual Revision	No criteria changes.	10/18/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hereditary Angioedema – C1 Esterase Inhibitors (Intravenous) Utilization Management Medical 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.

Dosing Information for Plasma-Derived C1-INH (Berinert, Cinryze)

For prophylaxis (Berinert or Cinryze), the maximum allowable dose in the policy comes from the Cinryze prescribing information and is applied to both Berinert and Cinryze prophylactic use requests. For the acute setting (Berinert or Cinryze), dosing recommendations come from the Berinert prescribing information and are applied to both Berinert and Cinryze requests for acute use. Of note, in the pivotal study of Berinert, a maximum of 20 IU/kg of Berinert was administered, and response was assessed for up to 24 hours. For the treatment of acute attacks, the prescribing information states that doses of Berinert lower than 20 IU/kg should not be administered.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Berinert, Cinryze, and Ruconest. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Berinert, Cinryze, and 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. 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

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1. 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.

Dosing. Approve one of the following regimens (A or B):

A) Patient is ≥ 12 years of age: Approve up to a maximum dose of 2,500 units (not exceeding 100 units/kg), administered intravenously no more frequently than twice weekly with doses separated by at least 3 days; OR

B) Patient is < 12 years of age: Approve up to a maximum dose of 1,000 units, administered intravenously no more frequently than twice weekly with doses separated by at least 3 days.

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2. 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.

Dosing. Approve 20 IU/kg, administered intravenously no more frequently than once daily.

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

FDA-Approved Indication

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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.

Dosing. Approve up to a maximum dose of 4,200 units (not exceeding 50 units/kg), administered intravenously no more frequently than twice daily.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Berinert, Cinryze, or Ruconest is not recommended in the following situations:

1. **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.

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. Berinert® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; September 2021.
2. Cinryze® intravenous infusion [prescribing information]. Lexington, MA: Takeda; January 2021.
3. Ruconest® intravenous infusion [prescribing information]. Warren, NJ: Pharming; April 2020.
4. Zuraw BL. Hereditary angioedema. *N Engl J Med*. 2008;359:1027-1036.
5. 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.
6. 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.
7. 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.
8. 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Selected Revision	**Berinert and Cinryze** **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Prophylaxis:** A Note was added to the initial and continuation criteria that a diagnosis of HAE with normal C1-INH (also known as HAE type III) does not satisfy the requirement for a diagnosis of HAE type I or type II. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Treatment of Acute Attacks:** A Note was added to the initial and continuation criteria that a diagnosis of HAE with normal C1-INH (also known as HAE type III) does not satisfy the requirement for a diagnosis of HAE type I or type II. **Ruconest** **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Treatment of Acute Attacks:** A Note was added to the initial and continuation criteria that a diagnosis of HAE with normal C1-INH (also known as HAE type III) does not satisfy the requirement for a diagnosis of HAE type I or type II.	06/01/2022
Annual Revision	**Berinert and Cinryze** **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Prophylaxis:** In Dosing, the interval was revised to read "no more frequently than twice weekly with doses separated by at least 3 days". Previously, the interval was written as "no more frequently than once every 3 days".	09/21/2022
Annual Revision	It was added to the Policy Statement that a person who has previously met initial therapy criteria for Cinryze, Berinert, or Ruconest for the requested indication under the Coverage Review Department and is currently receiving the medication, is only required to meet continuation of therapy criteria. If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Cinryze, Berinert, or Ruconest, initial therapy criteria must be met. In addition, the following changes were made: **Berinert and Cinryze** **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Prophylaxis:** Deleted [Type I or Type II] from indication heading. Under criteria for "Patient is currently receiving Berinert or Cinryze prophylaxis", added a Note that patient has to meet initial therapy criteria and approval through the Coverage Review Department if they had previously received initial therapy approval through a different entity. Also added the word "type" before II while referring to diagnosis of HAE types. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Treatment of Acute Attacks:** Deleted [Type I or Type II] from indication heading. Under criteria for "Patient has treated previous acute HAE attacks with Berinert or Cinryze", added a Note that patient has to meet initial therapy criteria and approval through the Coverage Review Department if they had previously received initial therapy approval through a different entity. **Ruconest** **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Treatment of Acute Attacks:** Deleted [Type I or Type II] from indication heading. Under criteria for "Patient has treated previous acute HAE attacks with Ruconest", added a Note that patient has to meet initial therapy criteria and approval through the Coverage Review Department if they had previously received initial therapy approval through a different entity.	09/20/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hereditary Angioedema – C1 Esterase Inhibitors (Subcutaneous) Utilization Management Medical 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 medical benefit coverage of Haegarda. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 required 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):
   - **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 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.

   Dosing. Approve up to a maximum dose of 60 IU/kg per injection, administered subcutaneously no more frequently than twice weekly with doses separated by at least 3 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Haegarda is not recommended in the following situations:

1. **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).

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. Haegarda® subcutaneous injection [prescribing information]. Kankakee, IL: CSL Behring; January 2022.
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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Selected Revision	**Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Prophylaxis:** A Note was added to the initial and continuation criteria that a diagnosis of HAE with normal C1-INH (also known as HAE type III) does not satisfy the requirement for a diagnosis of HAE type I or type II.	06/01/2022
Annual Revision	**Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Prophylaxis:** In Dosing, the interval was revised to read "no more frequently than twice weekly with doses separated by at least 3 days". Previously, the interval was written as "no more frequently than once every 3 days".	09/21/2022
Annual Revision	It was added to the Policy Statement that a person who has previously met initial therapy criteria for Haegarda for the requested indication under the Coverage Review Department and is currently receiving Haegarda, is only required to meet continuation of therapy criteria (i.e., patient is currently receiving Haegarda). If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Haegarda, initial criteria must be met. In addition, the following changes were made: **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Prophylaxis:** Deleted [Type I or Type II] from indication heading. Under criteria for "Patient is currently receiving Haegarda prophylaxis", added a Note that patient has to meet initial therapy criteria and approval through the Coverage Review Department if they had previously received initial therapy approval through a different entity. Also added the word "type" before II while referring to diagnosis of HAE types.	09/20/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hereditary Angioedema – Kalbitor Utilization Management Medical 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 medical benefit coverage of Kalbitor. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kalbitor, 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. 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

1. **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):
   - **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 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.
     - **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 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.
     - **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.

   Dosing. Approve up to a maximum dose of 30 mg per injection, administered subcutaneously no more frequently than twice daily.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kalbitor is not recommended in the following situations:

1. **Hereditary Angioedema (HAE) Prophylaxis**. Data are not available and Kalbitor is not indicated for prophylaxis of HAE attacks.

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. Kalbitor® subcutaneous injection [prescribing information]. Lexington, MA: Takeda; 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	09/21/2022
Annual Revision	It was added to the Policy Statement that a person who has previously met initial therapy criteria for Kalbitor for the requested indication under the Coverage Review Department and has treated previous HAE attacks with Kalbitor, is only required to meet the continuation of therapy criteria (i.e., patient has treated previous 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 criteria must be met. In addition, the following changes were made: **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Treatment of Acute Attacks:** Deleted [Type I or Type II] from indication heading. Under criteria for "Patient who has treated previous HAE attacks with Kalbitor", added a Note that patient has to meet initial therapy criteria and approval through the Coverage Review Department if they had previously received initial therapy approval through another entity. Also added the word "type" before II while referring to diagnosis of HAE types.	09/20/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Homozygous Familial Hypercholesterolemia – Evkeeza Utilization Management Medical 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 medical benefit coverage of Evkeeza. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **Homozygous Familial Hypercholesterolemia.** 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 ≥ 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

B) 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.

Dosing. Approve 15 mg/kg administered by intravenous infusion no more frequently than once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Evkeeza is not recommended in the following situations:

1. **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]

2. **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.

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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Homozygous Familial Hypercholesterolemia:** Praluent was added as an example of a proprotein convertase subtilisin kexin type 9 inhibitor used for homozygous familial hypercholesterolemia.	02/23/2022
Annual Revision	No criteria changes.	03/08/2023
Selected Revision	**Homozygous Familial Hypercholesterolemia:** The age of approval was changed to ≥ 5 years of age; previously, a patient had to be ≥ 12 years of age. Also, criteria were revised to not require a patient 5 to 9 years of age to try one proprotein convertase subtilisin kexin type 9 inhibitor.	03/29/2023
Early Annual Revision	It was added to the Policy Statement that 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 criteria must be met. In addition, the following changes were made: **Homozygous Familial Hypercholesterolemia:** Requirements were divided to distinguish between initial therapy and patient currently receiving Evkeeza (previously there was only one criteria set). For a patient who is currently receiving Evkeeza and has previously met initial therapy criteria for the requested indication under the Coverage Review Department, only the continuation of therapy criteria has to be met. The continuation of therapy criteria states that according to the prescribing physician, the patient has experienced a response to therapy with examples provided in a Note.	04/26/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Human Immunodeficiency Virus – Cabenuva Utilization Management Medical Policy

- Cabenuva® (cabotegravir extended-release intramuscular injection; rilpivirine extended-release intramuscular injection, co-packaged – ViiV/GlaxoSmithKline)

REVIEW DATE: 02/01/2023

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 ≥ 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.[1]

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]

Vocabria + Edurant Lead-In (at Least 28 Days)	Cabenuva Initiation Injections (One-Time Dosing)	Cabenuva Continuation Injections (Once-Monthly Dosing)
Month 1	At Month 2 (On the Last Day of Oral Lead-In Dosing)	Month 3 Onwards
Vocabria (30 mg) QD with a meal	cabotegravir 600 mg (3 mL)	cabotegravir 400 mg (2 mL)
Edurant (25 mg) QD with a meal	rilpivirine 900 mg (3 mL)	rilpivirine 600 mg (2 mL)

QD – Once daily.

Table 2. Recommended Oral Lead-In and Every 2 Month Intramuscular Injection Dosing Schedule.[1]

Vocabria + Edurant Lead-In (at Least 28 Days)	Cabenuva Initiation Dosing	Cabenuva Continuation Injections (Once Every 2 Month Dosing)
Month 1	At Month 2 and Month 3	Month 5 Onwards
Vocabria (30 mg) QD with a meal	cabotegravir 600 mg (3 mL)	cabotegravir 600 mg (3 mL)
Edurant (25 mg) QD with a meal	rilpivirine 900 mg (3 mL)	rilpivirine 900 mg (3 mL)

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 ever 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 history of treatment failure and no known or suspected resistance to either agent included in 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 medical benefit coverage of Cabenuva. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **Human Immunodeficiency Virus (HIV)-1, Treatment.** 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 (i, ii, iii, iv, v, and vi):
     - **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.** According to the prescriber, the patient meets ONE of the following (a or b):

a) Patient has difficulty maintaining compliance with a daily antiretroviral regimen for HIV-1; OR

b) Patient has severe gastrointestinal issues that may limit absorption or tolerance of oral medications; 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 Cabenuva. Approve if the patient has HIV-1 RNA < 50 copies/mL (viral suppression) **[documentation required]**.

Dosing. Approve one of the following dosing regimens (A or B):

A) Once Monthly Dosing Regimen: Approve 600 mg/900 mg intramuscularly for one dose, then approve 400 mg/600 mg intramuscularly once-monthly thereafter (every 4 weeks).

B) Every 2 Months Dosing Regimen: Approve 600 mg/900 mg intramuscularly for two doses, 1 month apart, then approve 600 mg/900 mg intramuscularly once every 2 months thereafter (every 8 weeks).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cabenuva is not recommended in the following situations:

1. **Pre-Exposure Prophylaxis (PrEP) of Human Immunodeficiency Virus (HIV)-1 Infection.** Cabenuva is not indicated for the prevention of HIV.

2. **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]

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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Human Immunodeficiency Virus Type-1 (HIV-1), Treatment:** The indication was modified to as listed to add the qualifier "-1" and "treatment" after HIV. Criteria requiring the patient completed/would complete 1 month of therapy with Vocabria (cabotegravir tablets) + Edurant (rilpivirine tablets), was removed. Cabenuva was added to criteria requiring that prior to initiating therapy with "Cabenuva" or 1 month lead-in with Vocabria the patient was treated with a stable regimen (≥ 4 months) of antiretrovirals for HIV-1. **Conditions Not Recommended for Coverage: Pre-Exposure Prophylaxis (PrEP) of Human Immunodeficiency Virus (HIV)-1 Infection** was modified to as listed to add the qualifier "of Human Immunodeficiency Virus (HIV)-1 Infection" after PrEP. **Human Immunodeficiency Virus (HIV), Antiretroviral Treatment-Naïve Patients** was removed because it was not needed. **Co-administration with Antiretrovirals for Human Immunodeficiency Virus (HIV) Treatment** was modified to as listed to add the qualifier "treatment" after HIV.	02/09/2022
Selected Revision	**Human Immunodeficiency Virus Type-1 (HIV-1), Treatment:** The age indication for approval was changed to ≥ 12 years of age and ≥ 35 kg. Previously the age of approval was ≥ 18 years of age.	04/06/2022
Annual Revision	No criteria changes.	02/01/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Human Immunodeficiency Virus – Sunlenca Prior Authorization Policy
- Sunlenca® (lenacapavir subcutaneous injection – Gilead)

REVIEW DATE: 01/04/2023; selected revision 04/12/2023

OVERVIEW

Sunlenca, a human immunodeficiency virus type 1 (HIV-1) capsid inhibitor, is indicated in combination with other antiretroviral(s) for the treatment of HIV-1 infection in heavily treatment-experienced adults with **multidrug resistant HIV-1 infection** failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.[1] Of note, Sunlenca is also available as tablets which are not addressed in this policy.

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.

Dosing

Initial treatment with Sunlenca has two scheduling options. Option 1: Two subcutaneous (SC) injections (927mg) and two tablets (600 mg) on Day 1, then two tablets (600 mg) on Day 2. Option 2: Two tablets (600 mg) on Days 1 and 2, one tablet (300 mg) on Day 8, and two SC injections (927 mg) on Day 15. For either option, maintenance treatment begins 26 weeks (± 2 weeks) after the initial dosing regimen is completed and continues as two SC injections (927 mg) once every 6 months (Q6M). Injections are given by a healthcare provider. Missed dose. During the maintenance period, if > 28 weeks have elapsed since the last injection and if clinically appropriate to continue Sunlenca treatment, restart the initiation dosage regimen from Day 1 using either Option 1 or Option 2.

Guidelines

Sunlenca is not addressed as an approved agent in guidelines.[4,5] According to the Department of Health and Human Services Guidelines for the use of antiretroviral s in adults and adolescents with HIV (January 20, 2022), in patients with multidrug resistance without fully active antiretroviral options, consensus on optimal management is lacking.[4] 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 Trogarzo® (ibalizumab-uiyk

intravenous injection) and/or Rukobia™ (fostemsavir extended-release tablets). Sunlenca is only mentioned as an agent in clinical trials, but not approved.

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 medical benefit coverage of Sunlenca. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 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

1. **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 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.** 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 inhibitor 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.

B) Patient is Currently Receiving Sunlenca. Approve for 1 year if the patient meets BOTH 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 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.

Dosing. Approve an initial dose of 927 mg subcutaneously one time, and maintenance dose of 927 mg subcutaneously every 6 months (± 2 weeks from the date of the last injection).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sunlenca is not recommended in the following situations:

1. **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).[2]

2. **Human Immunodeficiency Virus (HIV), Use in Treatment-Naïve Patients.** Sunlenca is not approved for this indication; however, it is under investigation in one Phase II, unpublished, and ongoing clinical trial in treatment-naïve adults with HIV-1 (CALIBRATE).[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.

REFERENCES

1. Sunlenca® tablets and subcutaneous injection [prescribing information]. Foster City, CA: Gilead; December 2022.
2. Segal-Maurer S, DeJesus E, Stelbrinka HJ; for the CAPELLA Study Investigators. Capsid inhibition with lenacapavir in multidrug-resistant HIV-1 infection. *N Engl J Med.* 2022; 1793-1803.
3. Gupta SK, Sims J, Brinson C, et al. Lenacapavir as part of a combination regimen in treatment-naïve people with HIV: Week 54 results [poster]. Presented at: CROI 2022; Virtual Event; February 12-16, 2022.
4. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. Last Updated: September 21, 2022. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf. Accessed December 26, 2022.
5. Gandhi RT, Bedimo R, Hoy JF, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults 2022 recommendations of the International Antiviral Society–USA Panel. *JAMA.* [Epub ahead of Print Dec 1, 2022].

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/04/2023
Selected Revision	**Human Immunodeficiency Virus (HIV)-1 Infection, Treatment**: Dosing was updated to approve an initial dose of 927 mg subcutaneously one time and a maintenance dose of 927 mg every 6 months (± 2 weeks from the date of the last injection). Previously, two dosing options were provided: an initial dose of 927 mg subcutaneously one time (Day 1), and maintenance dose of 927 mg subcutaneously every 6 months (26 weeks) from the date of the last injection ± 2 weeks; OR an initial dose of 927 mg two times (Day 1 and Day 15), and maintenance dose of 927 mg subcutaneously every 6 months (26 weeks) from the date of the last injection ± 2 weeks.	04/12/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Human Immunodeficiency Virus – Trogarzo Utilization Management Medical Policy
- Trogarzo® (ibalizumab-uiyk intravenous injection – Theratechnologies)

REVIEW DATE: 03/29/2023

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 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 medical benefit coverage of Trogarzo. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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1. Human Immunodeficiency Virus (HIV)-1. Approve for the duration outlined 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 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, elvitegravir.

f) CCR5-antagonist; AND
Note: An example of a CCR5-antagonist includes but it 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 BOTH 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.

Dosing. Approve the following dosing regimens (A and B):

A) Loading dose of 2,000 mg as an intravenous infusion given one time; AND
Note: Approve an additional 2,000 mg loading dose if an 800-mg maintenance dose is missed by ≥ 3 days of the scheduled dosing day, with maintenance dosing (800 mg intravenously every 2 weeks) resumed thereafter.

B) Maintenance dose of 800 mg, as an intravenous infusion or intravenous push, given every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Trogarzo is not recommended in the following situations:

1. **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]

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. Trogarzo® injection [prescribing information]. Montreal, Quebec, Canada: Theratechnologies; October 2022.
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3. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf. Accessed March 24, 2023. Updated March 23, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Human Immunodeficiency Virus (HIV)-1.** For initial therapy, the requirement that the patient is failing a current antiretroviral regimen according to the prescribing physician was changed to according to the prescriber. For the requirement of a response to therapy, according to the prescribing physician was changed to according to the prescriber.	04/06/2022
Selected Revision	**Human Immunodeficiency Virus (HIV)-1.** Dosing was updated to include maintenance dosing by intravenous push.	10/12/2022
Annual Revision	**Human Immunodeficiency Virus (HIV)-1 Infection:** Examples of antiretroviral therapies tried were moved to notes.	03/29/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Immune Globulin Intravenous Utilization Management Medical 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 infections in patients with hypogammaglobulinemia and/or recurrent infections.[6,18,21]
- **Chronic inflammatory demyelinating polyneuropathy (CIDP)**, to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.[7,9,12,15,67]
- **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] The American Heart Association and the American Academy of Pediatrics recommend initial therapy 2 g of IVIG per kg as a single intravenous (IV) dose given over 10 to 12 hours.[26] The dose can be repeated if needed.
- **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.[3,4,7-10,12,13,17,24,45]

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-CD20 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). Guidelines from the American Society for Blood and Marrow Transplantation make recommendations for IVIG dosing in HCT recipients to prevent infectious complications.[39] During the first 100 days after HCT, the dose in adults and adolescents is 0.5 g/kg per week. The IVIG dose should be individualized to maintain trough (pre-dose) serum IgG greater than 400 to 500 mg/dL. The dose in allogeneic pediatric HCT patients is 0.4 g/kg per month, adjusted to keep IgG > 400 mg/dL. Higher and more frequent dosing may be necessary in patients for prevention of early disease after HCT because the half-life of IVIG is reduced to between 1 to 10 days in this population. Dosing for > 100 days post-HCT is 0.5 g/kg given every 3 to 4 weeks. The dose is not adjusted using serum IgG level in patients with multiple myeloma or malignant macroglobulinemia. 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] four and five) 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 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. The international consensus guidance statement for myasthenia gravis[65] recommends an initial dose of 2 g/kg given in divided doses over 2 to 5 days. For maintenance therapy, the recommended dose is 0.4 to 1 g/kg given every 4 weeks; an attempt to decrease frequency can be made over time. If additional treatment is required, the dose should be adjusted based on the response.
- **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. ACIP recommends 400 mg/kg as an IV infusion.[13]

- **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, preferable within 4 days, and as late as 10 days after exposure.[47] In situations where administration of VariZIG does not appear possible within 10 days of exposure, IVIG is considered an alternative and should be given within 10 days of exposure[48] (and ideally within 96 hours of exposure).[40] The dose is 400 mg/kg given once.[40,41,46] 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. Recent reviews note that 200 to 400 mg/kg/day for 5 to 10 days is considered the recommended treatment course.[79]
- **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 medical benefit coverage of IVIG products. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 products as well as the monitoring required for adverse events and long-term efficacy, some approvals require IVIG products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

If the prescriber is switching between IVIG products and a case has already been approved by a clinician, a new approval may be entered without another clinical review. The new approval should only be extended for the remaining doses and duration which were granted on the original review. The indication (or diagnosis code) and dosing need to be the same as the original review. If the indication or dosing is different, a new clinical review would need to be completed.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of immune globulin intravenous products is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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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 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)]:
           Patient has an impaired antibody response (i.e., failure to product antibodies to specific antigens); OR
           - **(a)** 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 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: Examples of continued benefit with the product includes increased IgG levels or prevention and/or controlling of infections.

Dosing. Approve ONE of the following dosing regimens (A, B, C, or D):
A) An initial loading dose of 1 g/kg given intravenously one time; OR
B) 0.2 g/kg to 0.8 g/kg given intravenously once every 3 to 4 weeks; OR
C) The dose and interval between doses has been adjusted based on clinical response as determined by the prescriber; OR
D) Patients with primary immune deficiency and exposure to measles (previous exposure or risk of future measles exposure), the minimum dose has been determined by the prescriber.

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2. B-Cell Chronic Lymphocytic Leukemia for Prevention of Infections. 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 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.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 0.4 g/kg given intravenously every 3 to 4 weeks; OR
B) 0.3 g/kg to 0.5 g/kg given intravenously once monthly; OR
C) The dose and interval have been adjusted to maintain a trough (pre-dose) IgG level of greater than 500 mg/dL.

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3. 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.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) An initial loading dose of 2 g/kg given intravenously in divided doses over 2 to 4 consecutive days; OR
B) A maintenance dose of 1 g/kg given intravenously over one day or divided into two doses of 0.5 g/kg given on 2 consecutive days. Either regimen is given every 3 weeks; OR
C) The dose and interval are adjusted according to clinical response with a maximum dose per treatment course of 2 g/kg.

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4. 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 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 a 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.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) 2 g/kg given intravenously in divided doses over 2 to 5 consecutive days every 4 weeks; OR

B) 2 g/kg given intravenously in divided doses over 2 to 5 consecutive days every 2 to 3 weeks.

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5. 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.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) Up to 1 g/kg on 2 consecutive days OR up to 0.4 g/kg on 5 consecutive days (up to a total of 2 g per kg per treatment course); OR
B) The dose and interval between doses has been adjusted according to the platelet count and/or to prevent significant bleeding as determined by the prescriber.

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6. Kawasaki Disease. Approve for 3 months if prescribed by or in consultation with a pediatric cardiologist or a pediatric infectious diseases physician.

Dosing. Approve up to 2 g/kg given intravenously as a single dose or over multiple consecutive days. The dose may be repeated if needed.

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7. 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 probable motor conduction block; OR
    b) The prescriber has determined the patient has multifocal motor neuropathy without conduction block; OR
    c) The diagnosis is 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.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) Therapy is initiated with 2 g/kg given intravenously in divided doses over 2 to 5 consecutive days; OR
B) One of the following maintenance dosing regimen is used (i, ii, or iii):
  i. 0.5 g/kg to 2.4 g/kg given intravenously every month; OR
  ii. 1 g/kg given intravenously every 2 to 4 weeks; OR
  iii. 2 g/kg given intravenously every 1 to 2 months.

Other Uses with Supportive Evidence

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8. Antibody-Mediated Rejection in Transplantation. Approve for 1 year if prescribed by or in consultation with a physician affiliated with a transplant center.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) Up to 2 g/kg as an intravenous infusion (as a single dose or divided in smaller doses [e.g., 400 mg per kg daily for 5 days]); OR
B) The dosage is based on a transplant center's protocol.

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9. 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.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):

A) 2 g/kg per cycle given intravenously every 3 to 4 weeks. This dose is divided over 2, 3, or 5 consecutive days; OR

B) In patient with aggressive ocular disease, such as ocular cicatricial pemphigoid, 2 g/kg given intravenously may be given every 2 weeks in divided doses over 2, 3, or 5 consecutive days; OR

C) The frequency is gradually being slowly decreased as the lesions resolve and heal.

10. Cytomegalovirus Pneumonitis or Pneumonia in a Patient 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.

Dosing. Approve 400 mg/kg given intravenously every other day for 3 to 5 doses.

11. 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.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) Up to 2 g/kg per month administered intravenously (as a single dose or divided in smaller doses [e.g., 400 mg per kg daily for 5 days]); OR

B) The dosage is based on a transplant center's protocol.

12. 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 after 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 Barré 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.

Dosing. Approve 2 g/kg administered intravenously in divided doses over 2 to 5 days.

13. Hematologic Neoplasm-Associated Hypogammaglobulinemia or Hypogammaglobulinemia after B-cell Targeted Therapies (Secondary Immunodeficiency [SID]). 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 disease 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.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):

A) 0.4 g/kg to 0.6 g/kg given intravenously once a month; OR

B) 0.2 g/kg to 0.8 g/kg given intravenously once every 3 to 4 weeks; OR

C) The dose and interval between doses has been adjusted based on clinical response as determined by the prescriber.

14. 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.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):

A) During the first 100 days after HCT, the patient meets ONE of the following (i or ii):
- **i.** Adults and adolescents: 0.5 g/kg per week given intravenously and the dose is adjusted to maintain trough (pre-dose) serum IgG greater than 400 mg/dL; OR
- **ii.** Pediatric patient with allogeneic HCT: 0.4 g/kg per month given intravenously and the dose is adjusted to keep IgG greater than 400 mg/dL; OR

B) Greater than 100 days post-HCT, the dose is 0.5 g/kg given intravenously every 3 to 4 weeks, and the dose is adjusted to keep IgG greater than 400 mg/dL; OR

C) The dosage is based on a transplant center's protocol.

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15. 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 infection, a gastroenterologist, hepatologist, or a liver transplant physician.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) Up to 2 g/kg given intravenously in divided doses over 2 to 5 days; OR

B) Up to 1 g/kg one time given intravenously up to once weekly.

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16. 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.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) The dose is 0.4 g/kg given by intravenous infusion every 2 to 4 weeks; OR

B) The dose and interval are adjusted according to clinical effectiveness.
Note: Examples of adjusting according to clinical effectiveness may include the need to increase the dose or frequency based on frequency or severity of infections, hospitalizations, days of school or work missed, failure to thrive.

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17. 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.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):

A) Up to 0.4 g/kg given intravenously daily for 5 days; OR

B) Up to 2 g/kg given intravenously over 2 to 5 days; OR

C) The dose and interval between doses has been adjusted based on clinical response as determined by the prescriber.

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18. 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.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) Up to 2 g/kg given intravenously in divided doses over 2 to 5 consecutive days; OR

B) Maintenance therapy every 4 weeks with up to 2 g/kg with the dose being adjusted based on clinical symptoms.

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19. 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.

Dosing. Approve 0.4 g/kg to 0.5 g/kg given intravenously every 3 to 4 weeks.

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20. 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) 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; AND

C) The medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of MS.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) A single 1 g/kg given intravenously; OR

B) 0.4 g/kg per day IV infusion for 5 consecutive days.

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21. 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. Patient meets ONE of the following conditions (a, b, c, or d):

a) Patient has an exacerbation of myasthenia gravis; OR

b) Patient requires stabilization of myasthenia gravis before surgery; OR

c) 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) 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. Patient has refractory myasthenia gravis; AND

ii. Patient has tried pyridostigmine; AND

iii. 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 include improvement in weakness (bulbar, limb, or respiratory), improvement with ocular symptoms.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):

A) Short-term use: 2 g/kg given intravenously in divided doses over 2 to 5 consecutive days; OR

B) Maintenance therapy: 0.4 g/kg to 1 g/kg given intravenously every 4 weeks; OR

C) The dose and interval between doses has been adjusted based on clinical response as determined by the prescriber.

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22. 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 (i and ii):
i. Patient has been exposed to measles; AND
ii. Patient does not have evidence of immunity to measles (i.e., the patient does not have a history of the disease or age-appropriate vaccination); OR
B) Patient meets BOTH of the following (i and ii):
i. Patient is immunocompromised; AND
ii. Patient has been exposed to measles.

Dosing. Approve the following dosing regimen: 0.4 g/kg intravenously administered one time.

23. 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.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 0.4 g/kg given intravenously one time; OR
B) 0.2 to 0.4 g/kg given intravenously one time.

24. 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.

Dosing. Approve ONE of the following dosing regimens (A, B, C, or D):
A) 2 g/kg given intravenously over a period of 2 to 5 consecutive days; OR
B) 0.4 g/kg to 0.5 g/kg given intravenously daily for 5 days; OR
C) 0.4 g/kg given intravenously once every 4 weeks; OR
D) 0.2 g/kg to 0.4 g/kg given intravenously daily for 5 to 10 days

25. 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.

Dosing. Approve 0.5 g/kg given intravenously for 4 weeks.

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26. 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 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.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 2 g/kg given intravenously over a period of 2 to 5 consecutive days every month; OR
B) For maintenance therapy, the dose is adjusted to provide the minimum effective dosage of IVIG. Maximum dose is 2 g/kg given intravenously.

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27. 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.

Dosing. Approve ONE of the following dosing regimens (A, B, C, or D):
A) For the mother: 1 g/kg given intravenously every week; OR
B) For the mother: 2 g/kg given intravenously every week; OR
C) For the mother: 1 g/kg given intravenously twice weekly; OR
D) For the newborn: 1 g/kg to 2 g/kg given intravenously dosed per the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of immune globulin intravenous is not recommended in the following situations:

1. Adrenoleukodystrophy. Evidence does not support IVIG use.[18]

2. 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 with 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 establish efficacy, determine the optimal dosing regimen, and to confirm the safety of IVIG in the general AD population.[52,53]

3. **Amyotrophic Lateral Sclerosis.** There is insufficient evidence to recommend IVIG.[18]

4. **Asthma.** Global Initiative for Asthma (GINA) guidelines for asthma management and prevention do not include recommendations for use of IVIG.[54]

5. **Atopic Dermatitis.** Limited data exist to determine the utility of IVIG in the management of atopic dermatitis.[55]

6. **Autism.** Evidence does not support IVIG use.[18] Well controlled, double-blind trials are needed.

7. **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 difference was demonstrated.

8. **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.

9. **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.

10. **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]

11. **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.

12. **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.

13. **In Vitro Fertilization (IVF).** There is insufficient evidence to recommend IVIG administration as part of IVF outcomes.[68]

14. **Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes (POEMS) Syndrome.** Evidence does not support IVIG use.[18]

15. **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.[71] 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]

16. **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.

17. 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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**B-Cell Chronic Lymphocytic Leukemia for Prevention of Infections; Hematologic Neoplasm-Associated Hypogammaglobulinemia or Hypogammaglobulinemia after B-cell Targeted Therapies (Secondary Immunodeficiency); Hematopoietic Cell Transplantation to Prevent Infection: P**atient's immunoglobulin G (IgG) level was updated to < 600 mg/dL (6.0 g/L); previously was 500 mg/dL (5.0 g/L). **Human Immunodeficiency Virus (HIV) - or Hepatitis C-Associated Thrombocytopenia.** The diagnosis Hepatitis C-Associated Thrombocytopenia was added to the policy. Criterion was updated from patient is receiving combination antiretroviral therapy to patient is receiving antiviral therapy. Criteria related to clinically significant bleeding complications according to the prescriber was removed. Criterion regarding prescribing or consultation specialist was updated to include a gastroenterologist, a hepatologist, or a liver transplant physician. **Multiple Myeloma.** Added the wording, "or is at risk of" to the criterion related to severe recurrent infections according to the prescriber. **Post-Exposure Prophylaxis for Varicella:** The diagnosis wording was previously Passive Immunization for Varicella (Chickenpox) [Post-Exposure Prophylaxis]. The following criteria were removed: 1) Patient has HIV; Patient is immune compromised; Patient is pregnant; 2) Patient does not have evidence of immunity to varicella; 3) The specialist requirement. Also, Treatment or Post-Exposure Prophylaxis for Tetanus was added to the diagnosis with the following criterion: Tetanus Immune globulin is not available. Dosage of 0.2 to 0.4 g/kg intravenously one time was added. **Parvovirus B19 Infection:** Diagnosis wording was previously Pure Red Blood Cell Aplasia (PRCA) Secondary to Chronic (Persistent) Parvovirus B19 Infection. The word "chronic" immunodeficiency condition was removed from initial therapy criteria. The criterion regarding "clinically significant anemia as determined by the prescriber" and "patient is transfusion dependent" was removed. Continuation of therapy criteria related to hemoglobin and relapse were removed from the criteria. Removed "(one course) for up to two courses" from the dosage 2g/kg given intravenously over a period of 2 to 5 consecutive days. **Heart Failure, Chronic; Human Immunodeficiency Virus (HIV) Infection, Adults, for Prophylaxis of Infections; and Post-Polio Syndrome** were removed from Conditions Not Recommended for Approval	10/12/2022
Annual Revision	**Cytomegalovirus Pneumonitis or Pneumonia in a Patient with Cancer or Transplant-Related Infection:** Added the wording pneumonitis; the diagnosis wording was previously Cytomegalovirus Pneumonia in a Patient with Cancer or Transplant-Related Infection. **Multiple Myeloma:** The following option for approval was added in initial therapy as an alternative to infection status 1) Patient will be starting, has taken, or is currently receiving chimeric antigen receptor (CAR)-T cell therapy OR bispecific antibody therapy. Note: Examples of CAR-T cell therapy includes: Abecma (idecabtagene vicleucel intravenous infusion), Carvykti (ciltacabtagene autoleucel intravenous infusion). Note: Examples of bispecific antibody therapy includes: Elrexfio (elranatamab-bcmm	10/25/2023

	subcutaneous injection), Tecvayli (teclistamab-cqyv subcutaneous injection), Talvey (talquetamab-tgvs subcutaneous injection). **Parvovirus B19 Infection:** 0.2 g/kg to 0.4 g/kg given intravenously daily for 5 to 10 days was added as an alternative dosing regimen. **Anemia, Aplastic** was removed from Condition Not Recommended for Approval.	

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Immune Globulin Subcutaneous Utilization Management Medical 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 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.[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 (IV) 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 medical benefit coverage of SCIG products. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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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) The 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.

Dosing. Approve ONE of the following dosing regimens (A, B, C, D, or E):

A) The patient is transitioning from immune globulin intravenous (IVIG), and the maintenance dose (given once weekly, every 2 weeks, or more frequently than once weekly [e.g., 2 to 7 times per week]) is based on the patient's previous monthly IVIG dose; OR
B) The patient is transitioning from another immune globulin subcutaneous (SCIG) product, and the maintenance dose (given once weekly, every 2 weeks, or more frequently than once weekly) is based on the patient's previous weekly SCIG dose; OR
C) The patient is initiating SCIG therapy without previous IVIG or SCIG therapy and is receiving a loading dose (e.g., 100 mg/kg once daily for 5 consecutive days) followed by once weekly (or more frequently as necessitated by volume) maintenance dosing; OR
D) The dose and interval between doses has been adjusted based on clinical response, as determined by the prescriber; OR
E) For a patient with primary immune deficiency and exposure to measles (previous exposure or risk of future measles exposure), the minimum dose has been determined by the prescriber.

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2. 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 ALL of the following (i, ii, and iii):
i. 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.
B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has a clinically significant improvement in neurological 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.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) The dose is either 0.2 g/kg or 0.4 g/kg per week administered in one or two sessions over 1 or 2 consecutive days; OR
B) The dose and interval between doses has been titrated and adjusted based on clinical response as determined by the prescriber.

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

FDA-Approved Indication

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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: Examples of receiving benefit with the product includes increased IgG levels or prevention and/or controlling of infections.

Dosing. Approve ONE of the following dosing regimens for HyQvia (A, B, or C):

A) Patient is starting HyQvia and the dose and interval is being ramped-up to determine tolerability; OR
Note: The patient may be switching from immune globulin intravenous (IVIG) or from another SCIG product OR the patient may be naïve to immune globulin therapy. See prescribing information for ramp-up schedule.

B) Patient has already been started on HyQvia after the initial dose ramp-up and ONE of the following applies (i, ii, or iii):
- **i.** The dose is 300 mg/kg to 600 mg/kg given at 3 to 4 week intervals; OR
- **ii.** The dose and frequency is the same as previously used when receiving IVIG; OR
- **iii.** The dose and interval between doses has been adjusted based on clinical response as determine by the prescribing physician.

C) For a patient with primary immune deficiency and exposure to measles (previous exposure or risk of future measles exposure), the minimum dose has been determined by the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of immune globulin subcutaneous is not recommended in the following situations:

1. **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 immunoglobulin M (IgM) levels in a patient greater than 4 years of age in whom other causes of hypogammaglobulinemia have been excluded.[24] Selective IgA

deficiency may co-exist in some patients with poor specific IgG antibody production, with or without IgG2 subclass deficiency.[15,24] Some of these patients with a concomitant specific antibody defect might benefit from therapy with SCIG.

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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	10/12/2022
Selected Revision	HyQvia: Removal of age criteria. No dosing updates needed.	4/19/2023
Annual Revision	No criteria changes.	10/25/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Immunologicals – Cinqair Utilization Management Medical 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 medical benefit coverage of Cinqair. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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. 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

FDA-Approved Indication

1. Asthma. Approve Cinqair 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 ≥ 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):

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.

B) 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.

Dosing. Approve 3 mg/kg administered intravenously once every 4 weeks.

Conditions Not Recommended for Approval

Coverage of Cinqair is not recommended in the following situations:

1. **Concurrent use of Cinqair 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.

2. **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.

3. **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.

4. **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.

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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	03/16/2022
Selected Revision	**Asthma:** Criteria for a blood eosinophil level ≥ 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to any anti-interleukin-5 therapy was changed to prior to any treatment with Cinqair or another monoclonal antibody therapy that may lower blood eosinophil levels. Throughout criteria, updated notes to include examples of monoclonal antibody therapies to include Dupixent (dupilumab subcutaneous injection), Tezspire (tezepelumab-ekko subcutaneous injection), Adbry (tralokinumab-ldrm subcutaneous injection), and Xolair® (omalizumab subcutaneous injection). Criteria requiring the patient to have experienced one or more asthma exacerbation(s) requiring a hospitalization or an emergency department visit in the previous year, were updated to include an urgent care visit as well. **Conditions Not Recommended for Approval:** Criteria were updated to recommend against use of Cinqair with another monoclonal antibody therapy. Previously, criteria listed anti-interleukin monoclonal antibody therapies and Xolair separately.	07/20/2022
Annual Revision	**Conditions not recommended for approval:** Criteria were updated to clarify that use of Cinqair with another monoclonal antibody therapy is specific to Fasenra, Nucala, Dupixent, Tezspire, Xolair, and Adbry.	03/22/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Immunologicals – Fasenra Utilization Management Medical 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 beta$_2$-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:

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: forced expiratory volume in 1 second (FEV_1) < 80% predicted after appropriate bronchodilator withholding.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Fasenra. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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. 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

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1. Asthma. Approve Fasenra 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 ≥ 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

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):

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.

B) 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.

Dosing. Approve the following dosing regimens (A or B):
A) 30 mg administered subcutaneously once every 4 weeks for the first 3 doses; OR
B) 30 mg administered subcutaneously once every 8 weeks.

Conditions Not Recommended for Approval

Coverage of Fasenra is not recommended in the following situations:

1. **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 ≥ 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 (2023) note the negative data with Fasenra and state that further studies are needed.[10]

2. **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.

3. **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.

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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	03/16/2022
Selected Revision	**Asthma:** Criteria for a blood eosinophil level ≥ 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to any anti-interleukin-5 therapy was changed to prior to any treatment with Cinqair or another monoclonal antibody therapy that may lower blood eosinophil levels. Throughout criteria, updated notes to include examples of monoclonal antibody therapies to include Dupixent (dupilumab subcutaneous injection), Tezspire (tezepelumab-ekko subcutaneous injection), Adbry (tralokinumab-ldrm subcutaneous injection), and Xolair (omalizumab subcutaneous injection). Criteria requiring the patient to have experienced one or more asthma exacerbation(s) requiring a hospitalization or an emergency department visit in the previous year, were updated to include an urgent care visit as well. **Conditions Not Recommended for Approval:** Criteria were updated to recommend against use of Fasenra with another monoclonal antibody therapy. Previously, criteria listed anti-interleukin monoclonal antibody therapies and Xolair separately.	07/20/2022
Annual Revision	**Conditions not recommended for approval:** Criteria were updated to clarify that use of Fasenra with another monoclonal antibody therapy is specific to Cinqair, Nucala, Dupixent, Tezspire, Xolair, and Adbry.	03/22/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Immunologicals – Nucala Utilization Management Medical 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:

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: 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 medical benefit coverage of Nucala. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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. 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):

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 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), 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 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):

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.

B) 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.

Dosing. Approve one of the following dosing regimens (A or B):

A) If the patient is ≥ 12 years of age, approve 100 mg administered subcutaneously once every 4 weeks; OR

B) If the patient is 6 to 11 years of age, approve 40 mg administered subcutaneously once every 4 weeks.

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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):

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. 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.

B) 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.

Dosing. Approve 300 mg administered subcutaneously once every 4 weeks.

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3) Hypereosinophilic Syndrome. Approve Nucala for the duration noted if the patient meets one of the following conditions (A or B):

A) 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

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.

B) 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.

Dosing. Approve 300 mg administered subcutaneously once every 4 weeks.

4) Nasal Polyps. Approve Nucala 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):

a) Patient has received at least 3 months of therapy with an intranasal corticosteroid; AND

b) Patient will continue to receive therapy with an intranasal corticosteroid concomitantly with Nucala; 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) Nucala 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 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 4A [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 Nucala therapy are reduced nasal polyp size, improved nasal congestion, reduced sinus opacification, decreased sino-nasal symptoms, improved sense of smell.

Dosing. Approve 100 mg administered subcutaneously once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nucala is not recommended in the following situations:

1. **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.

2. **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 history. 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.

3. **Concurrent use of Nucala 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.

4. **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.

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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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual Revision	No criteria changes.	03/16/2022
Selected Revision	**Asthma:** Criteria for a blood eosinophil level ≥ 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to any anti-interleukin-5 therapy was changed to prior to any treatment with Nucala or another monoclonal antibody therapy that may lower blood eosinophil levels. Throughout criteria, updated notes to include examples of monoclonal antibody therapies to include Tezspire (tezepelumab subcutaneous injection), Adbry (tralokinumab-ldrm subcutaneous injection), Dupixent (dupilumab subcutaneous injection), and Xolair (omalizumab subcutaneous injection). Criteria requiring the patient to have experienced one or more asthma exacerbation(s) requiring a hospitalization or an emergency department visit in the previous year, were updated to include an urgent care visit as well. **Eosinophilic Granulomatosis with Polyangiitis (EGPA):** Criteria for a blood eosinophil level ≥ 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to any anti-interleukin-5 therapy was changed to prior to any treatment with any monoclonal antibody therapy that may lower blood eosinophil levels. **Hypereosinophilic Syndrome:** Criteria for a blood eosinophil level ≥ 1,000 cells per microliter prior to any anti-interleukin-5 therapy was changed to prior to any treatment with any monoclonal antibody therapy that may lower blood eosinophil levels. **Conditions Not Recommended for Approval:** Criteria were updated to recommend against use of Nucala with another monoclonal antibody therapy. Previously, criteria listed anti-interleukin monoclonal antibody therapies and Xolair separately.	07/20/2022
Annual Revision	**Conditions not recommended for approval:** Criteria were updated to clarify that use of Nucala with another monoclonal antibody therapy is specific to Cinqair, Fasenra, Dupixent, Tezspire, Xolair, and Adbry.	03/22/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Immunologicals – Tezspire Utilization Management Medical 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]

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:

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: forced expiratory volume in 1 second (FEV_1) < 80% predicted after appropriate bronchodilator withholding.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Tezspire. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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1. Asthma. Approve Tezspire 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, 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

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):

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.

B) 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.

Dosing. Approve 210 mg given subcutaneously once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tezspire is not recommended in the following situations:

1. **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]

2. **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.

3. **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.

4. **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.

5. **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.

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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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy		01/12/2022
Selected Revision	**Asthma:** Notes were updated to include Cinqair, Dupixent, Fasenra, Nucala, and Xolair as examples of monoclonal antibody therapies for asthma. Criteria requiring the patient to have experienced one or more asthma exacerbation(s) requiring a hospitalization or an emergency department visit in the previous year, were updated to include an urgent care visit as well.	07/20/2022
Annual Revision	**Conditions not recommended for approval:** For "Concurrent use of Tezspire with another Monoclonal Antibody Therapy", the condition was updated to specify that "other monoclonal antibody therapy" is defined as "Cinqair, Dupixent, Fasenra, Nucala, Xolair, and Adbry". There were no other changes to the criteria.	02/08/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Immunologicals – Xolair Utilization Management Medical 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:

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: 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 medical benefit coverage of Xolair. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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. 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, initial 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.

Dosing. Approve up to a maximum dose of 375 mg administered subcutaneously not more frequently than once every 2 weeks.

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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.

Dosing. Approve the following dosing regimens (A or B):
A) 150 mg administered subcutaneously once every 4 weeks; OR
B) 300 mg administered subcutaneously once every 4 weeks.

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3. **Nasal Polyps.** Approve Xolair 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 ≥ 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 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]).
      v. Patient meets BOTH of the following (a and b):
         a) Patient has received at least 3 months of therapy with an intranasal corticosteroid; AND
         b) Patient will continue to receive therapy with an intranasal corticosteroid concomitantly with Xolair; AND
      vi. 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
      vii. 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 Xolair. 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 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).
      ii. Patient continues to receive therapy with an intranasal corticosteroid; AND
      iii. 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.

Dosing. Approve up to a maximum dose of 600 mg administered subcutaneously not more frequently than once every 2 weeks.

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 (e.g., Cinqair, Fasenra, Nucala, Dupixent, Adbry, Tezspire) 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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	03/16/2022
Selected Revision	**Asthma:** Notes were updated to include Tezspire as an example of a monoclonal antibody therapy that may lower immunoglobulin E (IgE) levels and interfere with allergen testing. Notes were also updated to include Xolair, Cinqair, Fasenra, Nucala, and Tezspire as examples of monoclonal antibody therapies for asthma. Criteria requiring the patient to have experienced one or more asthma exacerbation(s) requiring a hospitalization or an emergency department visit in the previous year, were updated to include an urgent care visit as well. **Nasal Polyps**: Notes were updated to include Tezspire as an example of a monoclonal antibody therapy that may lower immunoglobulin E (IgE) levels and interfere with allergen testing. **Conditions Not Recommended for Approval:** Criteria were updated to recommend against use of Xolair with another monoclonal antibody therapy. Previously, criteria listed anti-interleukin monoclonal antibody therapies specifically.	07/20/2022
Annual Revision	**Conditions Not Recommended for Approval:** Criteria were updated to clarify that use of Xolair with another monoclonal antibody therapy is specific to Cinqair, Fasenra, Nucala, Dupixent, Tezspire, and Adbry.	03/22/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Inflammatory Conditions – Entyvio Intravenous Utilization Management Medical 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 medical benefit coverage of Entyvio intravenous. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted 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

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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
      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.

Dosing. Approve the following dosage regimen (A and B):
- **A)** The dose is 300 mg as an intravenous infusion at Weeks 0, 2, and 6; AND
- **B)** Subsequent doses are separated by at least 8 weeks.

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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
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
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.

2. Patient is Currently Receiving Entyvio (Intravenous or Subcutaneous). Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on Entyvio 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 Entyvio intravenous 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 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.

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.

Dosing. Approve the following dosage regimen (A and B):
A) The dose is 300 mg as an intravenous infusion at Weeks 0, 2, and 6; AND
B) Subsequent doses are separated by at least 8 weeks.

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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	06/28/2023
Early Annual Revision	**Ulcerative Colitis:** For a patient currently taking, it was clarified this applies to the intravenous or subcutaneous formulation. A note was added to clarify that a mesalamine product does not count as a systemic therapy for ulcerative colitis.	10/11/2023

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx® (secukinumab SC injection)	Inhibition of IL-17A	AS, ERA, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection, risankizumab-rzaa IV infusion)	Inhibition of IL-23	SC formulation: CD, PSA, PsO
		IV formulation: CD
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion, vedolizumab SC injection)	Integrin receptor antagonist	SC: UC
		IV: CD, UC
Oral Therapies/Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Cibinqo™ (abrocitinib tablets)	Inhibition of JAK pathways	AD
Olumiant® (baricitinib tablets)	Inhibition of JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of JAK pathways	AD, AS, nr-axSpA, RA, PsA, UC
Sotyktu™ (deucravacitinib tablets)	Inhibition of TYK2	PsO
Xeljanz® (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of JAK pathways	RA, PsA, UC

* 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.

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Inflammatory Conditions – Ilaris Utilization Management Medical 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.

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.

Guidelines

Ilaris is used for a variety of periodic fever syndromes and inflammatory conditions.

- **CAPS:** A consensus protocol for hereditary auto-inflammatory 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 medical benefit coverage of Ilaris. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the criteria and dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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1. Cryopyrin-Associated Periodic Syndromes (CAPS) [including Familial Cold Auto-inflammatory 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):

A) 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.

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 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.
    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.

Dosing. Approve one of the following dosing regimens (A or B):

A) Patient is ≥ 15 kg and ≤ 40 kg: Approve up to 3 mg/kg per dose administered subcutaneously no more frequently than once every 8 weeks; OR

B) Patient is > 40 kg: Approve up to 150 mg per dose administered subcutaneously no more frequently than once every 8 weeks.

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2. 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.

C) 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 decreased pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

Dosing. Approve one of the following dosing regimens (A or B):

A) Patient is ≤ 40 kg: Approve up to 4 mg/kg per dose administered subcutaneously no more frequently than once every 4 weeks; OR

B) Patient is > 40 kg: Approve up to 300 mg per dose administered subcutaneously no more frequently than once every 4 weeks.

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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):

i. 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

ii. 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.

Dosing. Approve up to 150 mg administered subcutaneously no more frequently than once every 12 weeks.

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.
    Note: Examples of improvement in symptoms include decreased pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

Dosing. Approve one of the following dosing regimens (A or B):

A) Patient is ≤ 40 kg: Approve up to 4 mg/kg per dose administered subcutaneously no more frequently than once every 4 weeks; OR

B) Patient is > 40 kg: Approve up to 300 mg per dose administered subcutaneously no more frequently than once every 4 weeks.

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):
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.
Note: Examples of improvement in symptoms include less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

Dosing. Approve up to 4 mg/kg to a maximum of 300 mg per dose administered subcutaneously no more frequently than once every 4 weeks.

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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):

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.
Note: Examples of improvement in symptoms include less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

Dosing. Approve up to 4 mg/kg to a maximum of 300 mg per dose administered subcutaneously no more frequently than once every 4 weeks.

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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 history 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):

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 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.
Note: Examples of improvement in symptoms include less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

Dosing. Approve one of the following dosing regimens (A or B):

A) Patient is ≤ 40 kg: Approve up to 4 mg/kg per dose administered subcutaneously no more frequently than once every 4 weeks; OR

B) Patient is > 40 kg: Approve up to 300 mg per dose administered subcutaneously no more frequently than once every 4 weeks.

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.

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.

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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HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Cryopyrin-Associated Periodic Syndromes (including Familial Cold Autoinflammatory Syndrome, Muckle-Wells Syndrome, and Neonatal Onset Multisystem Inflammatory Disease or Chronic Infantile Neurological Cutaneous and Articular Syndrome):** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving, it was clarified that this applies to a patient who is receiving for ≥ 6 months. A requirement was added for a patient who is currently receiving to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Familial Mediterranean Fever:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving, it was clarified that this applies to a patient who is receiving for ≥ 6 months. A requirement was added for a patient who is currently receiving to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving, it was clarified that this applies to a patient who is receiving for ≥ 6 months. A requirement was added for a patient who is currently receiving to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Stills Disease, Adult Onset:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving, it was clarified that this applies to a patient who is receiving for ≥ 6 months. A requirement was added for a patient who is currently receiving to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Systemic Juvenile Idiopathic Arthritis:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving, it was clarified that this applies to a patient who is receiving for ≥ 6 months. A requirement was added for a patient who is currently receiving to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Tumor Necrosis Factor Receptor Associated Periodic Syndrome:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving, it was clarified that this applies to a patient who is receiving for ≥ 6 months. A requirement was added for a patient who is currently receiving to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber.	02/16/2022
Annual Revision	No criteria changes.	01/25/2023
Selected Revision	**Gout, Acute Flare:** New condition of approval added.	09/06/2023

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PsA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx® (secukinumab SC injection)	Inhibition of IL-17A	AS, ERA, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection)	Inhibition of IL-23	PsA, PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC

* 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.

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Inflammatory Conditions – Ilumya Utilization Management Medical 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 medical benefit coverage of Ilumya. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the criteria and dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 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.

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.

Dosing. Approve the following dosing (A and B):

A) The dose is 100 mg given as a subcutaneous injection; AND

B) Doses are administered at Weeks 0 and 4, then not more frequently than once every 12 weeks thereafter.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ilumya 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 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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	05/11/2022
Annual Revision	No criteria changes.	05/10/2023

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PsA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx® (secukinumab SC injection)	Inhibition of IL-17A	AS, ERA, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection)	Inhibition of IL-23	PsA, PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Oral Therapies/Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Cibinqo™ (abrocitinib tablets)	Inhibition of JAK pathways	AD
Olumiant® (baricitinib tablets)	Inhibition of JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of JAK pathways	AD, AS, RA, PsA, UC
Xeljanz® (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of JAK pathways	RA, PsA, UC

* 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.

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Inflammatory Conditions – Infliximab Products Utilization Management Medical 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/Organon)

REVIEW DATE: 10/26/2022

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).[9] 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).[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 infliximab among the therapies for moderate to severe Crohn's disease, for induction and maintenance of remission.[5]
- **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.[6]
- **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.[7]
- **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.[8]
- **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]

Other Uses with Supportive Evidence

There are guidelines and/or published data supporting the use of infliximab products in the following conditions:

- **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 2.2022 – September 28, 2022] list infliximab among the agents used for steroid-refractory disease.[15]
- **Hidradenitis Suppurativa:** In a Phase II double-blind, placebo-controlled crossover trial, adult patients with moderate to severe hidradenitis suppurativa were randomized to placebo (n = 23) or infliximab 5 mg/kg (n = 15) at Weeks 0, 2, and 6.[16] Maintenance was continued through 22 weeks of treatment. Following Week 8, more patients in the infliximab-treatment group experienced a 50% or greater decrease in the Hidradenitis Suppurativa Severity Index (HSSI) score

(approximately 26% and 5% of patients receiving infliximab and placebo, respectively [data presented graphically]; P = 0.092). In post-hoc analysis, significantly more patients treated with infliximab responded with a 25% to < 50% response (60% and 5.6% for infliximab and placebo, respectively; P < 0.001). Improvement was noted through Week 30. In case series, infliximab has been effective in treating hidradenitis suppurativa that was refractory to other therapies.[17-19]

- **Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitors:** NCCN has guidelines (version 1.2022 – February 28, 2022) for Management of Immunotherapy-Related Toxicities.[20] 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).[21,22] 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. For oligoarthritis, a biologic is recommended following a trial of a conventional synthetic DMARD.[32] 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.[23] 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.[24]
- **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.[25] 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.[26] 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.[27,28] In case series, infliximab has been effective in patients with Still's disease that was refractory to therapy with corticosteroids, methotrexate, azathioprine, and cyclophosphamide.[29]

Dosing Information

The recommended dose of infliximab is weight-based and varies slightly by indication.[1-3] Dosing increase, interval shortening, or changing to another therapy is generally recommended for attenuation of response. Thus, published recommendations note that the dose and interval of infliximab may be adjusted, as needed, in patients who initially respond but then lose that response.[2] Additionally, data are emerging concerning tapering of infliximab dosage in patients with inflammatory conditions who are in remission or have low disease activity.[110-113] At this time, there is not a consensus regarding tapering. The 2015 ACR guidelines for RA mention tapering, defined as scaling back therapy (reducing dose or frequency) as a treatment option for patients who are in remission.[18] Although specific tapering schedules are not recommended, it is noted that minimizing therapy may decrease toxicity and lowers the risk of treating patients unnecessarily. When the dose of any RA therapy is tapered, it is recommended that there be a comprehensive plan to monitor disease activity and address possible flares.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of infliximab products. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 infliximab products as well as the monitoring required for adverse events and long-term efficacy, initial approval requires infliximab 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 infliximab 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.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 5 mg/kg as an intravenous infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then no more frequently than once every 6 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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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 criteria (i, ii, and iii):

i. Patient is ≥ 6 years of age; AND

ii. Patient meets ONE of the following conditions (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):

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 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 infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or blood in stool.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 5 mg/kg as an intravenous infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then no more frequently than once every 8 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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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 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 (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

iii. 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.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 5 mg/kg as an intravenous infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then no more frequently than once every 8 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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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 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 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.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 5 mg/kg as an intravenous infusion followed by additional similar doses 2 and 6 weeks after the first infusion, and then no more frequently than once every 8 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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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 criteria (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):
- **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)** 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.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 3 mg/kg as an intravenous infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then no more frequently than once every 8 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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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 criteria (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 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 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.

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 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.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 5 mg/kg as an intravenous infusion followed by additional similar doses 2 and 6 weeks after the first infusion, and then no more frequently than once every 8 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

Other Uses with Supportive Evidence

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7. 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 3 months if the patient meets BOTH of the following conditions (i and ii):

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

i. 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.

ii. 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).

Dosing. Approve the following regimens (A or B):
A) Initial Therapy. Approve up to 5 mg/kg as an intravenous infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, then no more frequently than once every 6 weeks thereafter.
B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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8. Graft-Versus-Host Disease. Approve for the duration noted if the patient meets ONE of the following criteria (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):
i. 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).
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: 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).

Dosing. Approve the following regimens (A and B):
A) The dose is up to 10 mg/kg given intravenously; AND
B) Doses are administered no more frequently than once weekly.

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9. 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 and ii):
i. Patient has tried one other therapy; AND
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):
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 include Hurley staging, Sartorius score, Physician Global Assessment, and Hidradenitis Suppurativa Severity Index.

iii. 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.

Dosing. Approve the following regimens (A and B):

A) Initial Therapy. Approve up to 5 mg/kg as an intravenous infusion followed by additional similar doses 2 and 6 weeks after the first infusion, and then no more frequently than once every 8 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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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):

A) 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.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 10 mg/kg as an intravenous infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, then no more frequently than once every 4 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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11. Indeterminate Colitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

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
  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):

- **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.
  - **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.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 5 mg/kg as an intravenous infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then no more frequently than once every 8 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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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):

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 criteria (i and ii):

- **i.** Patient meets ONE of the following conditions (a or b):

a) Patient has tried one other systemic medication for this condition; OR
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.
b) 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.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 6 mg/kg as an intravenous infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then no more frequently than once every 8 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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13. Pyoderma Gangrenosum. 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 conditions (i and ii):

i. Patient meets ONE of the following conditions (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):

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 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: size, depth, and/or number of lesions; AND

iii. 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.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 5 mg/kg as an intravenous infusion followed by additional similar doses 2 and 6 weeks after the first infusion, and then no more frequently than once every 8 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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14. Sarcoidosis. 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 conditions (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):

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 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 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.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 5 mg/kg as an intravenous infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, then no more frequently than once every 6 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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15. Scleritis or Sterile Corneal Ulceration. 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 conditions (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

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 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 eye pain, redness, light sensitivity, tearing, and/or improvement in visual acuity.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 10 mg/kg as an intravenous infusion administered at baseline and followed by up to three additional similar doses (for example, up to three additional doses given 2, 6, and 8 weeks after the initial infusion).

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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16. Spondyloarthritis, Other Subtypes Approve for the duration noted if the patient meets ONE of the following criteria (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.

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following conditions (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

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) 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.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 5 mg/kg as an intravenous infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then no more frequently than once every 6 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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17. Still'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 conditions (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):

i. 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).

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 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.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 6 mg/kg as an intravenous fusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then no more frequently than once every 8 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

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18. Uveitis. Approve for the duration noted if the patient meets ONE of the following criteria (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 conditions (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.

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 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 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.

Dosing. Approve the following regimens (A or B):

A) Initial Therapy. Approve up to 10 mg/kg as an intravenous infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, then no more frequently than once every 4 weeks thereafter.

B) Patient is Currently Receiving an Infliximab Product. Approve up to a maximum dose of 10 mg/kg administered intravenously no more frequently than once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of infliximab products is not recommended in the following situations:

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.

2. **Inflammatory Myopathies (Polymyositis, Dermatomyositis, Inclusion Body Myositis).** Exceptions are not recommended. In an open-label pilot study in 13 patients, four infliximab 5 mg/kg infusions given over 14 weeks were not effective in refractory inflammatory myopathies.[30] Infliximab could worsen muscle inflammation in these patients.

3. **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) recommend corticosteroids as first line therapy for giant cell arteritis.[31] For Takayasu's arteritis, corticosteroids and conventional synthetic DMARDS are listed as first-line therapy.

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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Juvenile Idiopathic Arthritis:** The approval condition was reworded to as listed. Previously the indication also included Juvenile Rheumatoid Arthritis (regardless of type of onset), which was moved into a Note. **Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy:** The requirement that the patient has an immunotherapy-related toxicity was reworded to generally refer to an immunotherapy-related toxicity other than hepatitis. Specific toxicities related to the gastrointestinal system, inflammatory arthritis, and ocular toxicity were moved from the criteria into a note representing examples of various immunotherapy-related toxicities. **Uveitis:** The approval condition was reworded to as listed. Previously, the indication included other posterior uveitides and panuveitis syndromes, which was moved into a note.	09/29/2021

Selected Revision	Infliximab intravenous infusion (authorized generic to Remicade) was added to the policy. Criteria are the same as the other infliximab products addressed in the policy.	12/08/2021
Annual Revision	**Ankylosing Spondylitis:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving an infliximab product to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Crohn's Disease:** Initial approval duration was changed to 6 months (previously was 3 months). Note was clarified to state that a previous trial of a biologic applies to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. A note was added to clarify that a trial of mesalamine does not count as a systemic agent for Crohn's disease. For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving an infliximab product to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Plaque Psoriasis:** Note was clarified to state that a previous trial of a biologic applies to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 90 days. Requirements were added that for a patient who is currently receiving an infliximab product, the patient must have at least one objective and at least one subjective response to therapy. Previously, response was more general and according to the prescriber. **Psoriatic Arthritis:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving an infliximab product to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Rheumatoid Arthritis:** Initial approval duration was changed to 6 months (previously was 3 months). Note was clarified to state that a previous trial of a biologic applies to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving an infliximab product to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Ulcerative Colitis:** Initial approval duration was changed to 6 months (previously was 3 months). Note was clarified to state that a previous trial of a biologic applies to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving an infliximab product to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Behcet's Disease:** Note was clarified to state that a previous trial of a biologic applies to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 90 days. Requirements were added that for a patient who is currently receiving an infliximab product, the patient must have at least one objective and at least one subjective response to therapy. Previously, response was more general and according to the prescriber. **Graft-Versus-Host Disease:** For a patient currently receiving, it was clarified that this applies to a patient who is receiving an infliximab product for ≥ 1 month. Requirements were added for a patient who is currently receiving, that there has been at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Hidradenitis Suppurativa:** For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an adalimumab product for ≥ 90 days. Requirements were added that for a patient who is currently receiving an	10/26/2022

	infliximab product, the patient must have at least one objective and at least one subjective response to therapy. Previously, response was more general and according to the prescriber. **Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving an infliximab product to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Indeterminate Colitis:** The definition of indeterminate colitis (colitis that cannot be classified with certainty as either ulcerative colitis or Crohn's disease) was moved to a note; previously this was included in the indication. Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving an infliximab product to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Juvenile Idiopathic Arthritis:** Initial approval duration was changed to 6 months (previously was 3 months). Note was clarified to state that a previous trial of a biologic applies to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving an infliximab product to have at least one objective or subjective response to therapy. For continuation, approvals were changed to be 1 year in duration. Previously, response was more general and according to the prescriber, and approvals were for 3 years. **Pyoderma Gangrenosum:** For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 4 months. Requirements were added that for a patient who is currently receiving an infliximab product, the patient must have at least one objective and at least one subjective response to therapy. Previously, response was more general and according to the prescriber. **Sarcoidosis:** To align with guidelines, the note that includes examples of immunosuppressive medications was updated to add leflunomide, mycophenolate mofetil, and hydroxychloroquine; cyclosporine, chlorambucil, and thalidomide were removed from the examples. Cardiologist and neurologist were added to the list of specialists who must prescribe or be consulted for this indication. For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 90 days. Requirements were added that for a patient who is currently receiving an infliximab product, the patient must have at least one objective and at least one subjective response to therapy. Previously, response was more general and according to the prescriber. **Scleritis or Sterile Corneal Ulceration:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving an infliximab product to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Spondyloarthritis, Other Subtypes:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving an infliximab product to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Still's Disease:** Initial approval duration was changed to 6 months (previously was 3 months). Note was updated to state that a previous trial of one biologic other than the requested drug counts towards a requirement for previous therapy. A biosimilar of the requested biologic does not count. For a patient currently receiving, it was clarified that this applies to a patient who is receiving an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving to have at least one	

	objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Uveitis:** Initial approval duration was changed to 6 months (previously was 3 months). Note was clarified to state that a previous trial of a biologic applies to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. For a patient currently receiving an infliximab product, it was clarified that this applies to a patient who has received an infliximab product for ≥ 6 months. A requirement was added for a patient who is currently receiving an infliximab product to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber.	

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx® (secukinumab SC injection)	Inhibition of IL-17A	AS, ERA, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection, risankizumab-rzaa IV infusion)	Inhibition of IL-23	SC formulation: CD, PSA, PsO
		IV formulation: CD
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Oral Therapies/Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Cibinqo™ (abrocitinib tablets)	Inhibition of JAK pathways	AD
Olumiant® (baricitinib tablets)	Inhibition of JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of JAK pathways	AD, AS, RA, PsA, UC
Sotyktu™ (deucravacitinib tablets)	Inhibition of TYK2	PsO
Xeljanz® (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of JAK pathways	RA, PsA, UC

* 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; Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Inflammatory Conditions – Simponi Aria Utilization Management Medical Policy
- Simponi Aria® (golimumab intravenous infusion – Janssen)

REVIEW DATE: 11/30/2022

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 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 American College of Rheumatology (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 medical benefit coverage of Simponi Aria. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Simponi Aria 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 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.

Dosing. Approve up to 2 mg/kg as an intravenous infusion at Weeks 0 and 4, then not more frequently than once every 8 weeks thereafter.

2. 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, 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 criteria (i and ii):
- **i.** Patient meets ONE of the following conditions (a or b):
  - **a)** Patient has tried one other medication for this condition; OR
    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.
  - **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 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.
  - **b)** 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.

Dosing. Approve up to 80 mg/m^2 as an intravenous infusion at Weeks 0 and 4, then not more frequently than once every 8 weeks thereafter.

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 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 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 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.

Dosing. Approve the following regimens (A or B):

A) Patient is ≥ 18 years of age: Approve up to 2 mg/kg as an intravenous infusion at Weeks 0 and 4, then not more frequently than once every 8 weeks thereafter; OR

B) Patient is < 18 years of age: Approve up to 80 mg/m^2 as an intravenous infusion at Weeks 0 and 4, then not more frequently than once every 8 weeks thereafter.

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4. 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 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 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) 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.

Dosing. Approve up to 2 mg/kg as an intravenous infusion at Weeks 0 and 4, then not more frequently than once every 8 weeks thereafter.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Simponi Aria is not recommended in the following situations:

1. **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.

2. **Ulcerative Colitis.** Simponi subcutaneous injection is indicated for treatment of ulcerative colitis.[5] 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.[6] Appropriate dosing of Simponi Aria in ulcerative colitis is unclear.

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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Juvenile Idiopathic Arthritis:** The approval condition was reworded to as listed. Previously the indication also included Juvenile Rheumatoid Arthritis (regardless of type of onset), which was moved into a Note.	11/03/2021
Annual Revision	**Ankylosing Spondylitis:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving Simponi Aria or subcutaneous, it was clarified that this applies to a patient who has received the product for ≥ 6 months. A requirement was added for a patient who is currently receiving Simponi Aria or subcutaneous to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Juvenile Idiopathic Arthritis:** Initial approval duration was changed to 6 months (previously was 3 months). Note was clarified to state that a previous trial of a biologic applies to at least one biologic other than the requested drug. For a patient currently receiving Simponi Aria or subcutaneous, it was clarified that this applies to a patient who has received the product for ≥ 6 months. A requirement was added for a patient who is currently receiving Simponi Aria or subcutaneous to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Psoriatic Arthritis:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving Simponi Aria or subcutaneous, it was clarified that this applies to a patient who has received the product for ≥ 6 months. A requirement was added for a patient who is currently receiving Simponi Aria or subcutaneous to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Rheumatoid Arthritis:** Initial approval duration was changed to 6 months (previously was 3 months). Note was clarified to state that a previous trial of a biologic applies to at least one biologic other than the requested drug. For a patient currently receiving Simponi Aria or subcutaneous, it was clarified that this applies to a patient who has received the product for ≥ 6 months. A requirement was added for a patient who is currently receiving Simponi Aria or subcutaneous to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber.	11/30/2022

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx® (secukinumab SC injection)	Inhibition of IL-17A	AS, ERA, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection, risankizumab-rzaa IV infusion)	Inhibition of IL-23	SC formulation: CD, PSA, PsO
		IV formulation: CD
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Oral Therapies/Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Cibinqo™ (abrocitinib tablets)	Inhibition of JAK pathways	AD
Olumiant® (baricitinib tablets)	Inhibition of JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of JAK pathways	AD, AS, nr-axSpA, RA, PsA, UC
Sotyktu™ (deucravacitinib tablets)	Inhibition of TYK2	PsO
Xeljanz® (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of JAK pathways	RA, PsA, UC

* 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.

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Inflammatory Conditions – Spevigo Utilization Management Medical 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]

Dosing Information
Spevigo is given as a single 900 mg dose by intravenous (IV) infusion over 90 minutes. If the generalized pustular psoriasis flare symptoms persist, an additional 900 mg dose given IV (over 90 minutes) may be administered one week after the initial dose.[1]

Guidelines
Spevigo is not listed in guidelines for generalized pustular psoriasis.

POLICY STATEMENT
Prior Authorization is recommended for medical benefit coverage of Spevigo. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for 1 month (30 days). Because of the specialized skills required for evaluation and diagnosis of patients treated with Spevigo approval requires Spevigo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

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

FDA-Approved Indication

1. **Generalized Pustular Psoriasis.** Approve for up to two doses if the patient meets ALL of the following (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient is experiencing a flare of a moderate-to-severe intensity and meets all of the following (i, ii, iii, and iv):
     - **i.** 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).
     - **ii.** Patient has a GPPGA pustulation subscore of ≥ 2 points; AND

iii. Patient has new or worsening pustules; AND
iv. Patient has erythema and pustules which affects ≥ 5% of body surface area; AND

C) If patient has already received Spevigo, patient meets both of the following (i and ii):
i. Patient has not already received two doses of Spevigo for treatment of the current flare; AND
ii. If this is a new flare, at least 12 weeks have elapsed since the last dose of Spevigo; AND

D) The medication is prescribed by or in consultation with a dermatologist.

Dosing. Approve the following dosing regimens (A, B, and C):
A) Approve 900 mg per dose administered by intravenous (IV) infusion; AND
B) If a second dose is administered, 7 days elapse between the doses; AND
C) If this a new flare, at least 12 weeks have elapsed since the last dose of Spevigo.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Spevigo is not recommended in the following situations:

1. **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.

2. **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.

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

1. Spevigo® intravenous infusion [prescribing information]. Ridgefield, CT: Boehringer Ingelheim; September 2022.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/07/2022
Selected Revision	**Conditions Not Recommended for Approval:** Concurrent Use with a Disease-modifying Antirheumatic Drug or Retinoid was removed. Concurrent Use with a Biologic was reworded to say "Concomitant Use with Another Biologic Prescribed for Treatment of Generalized Pustular Psoriasis." A note was added to clarify that a patient with concomitant plaque psoriasis and generalized pustular psoriasis may be receiving a biologic for treatment of plaque psoriasis.	09/28/2022
Annual Revision	No criteria changes.	10/04/2023

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PsA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx® (secukinumab SC injection)	Inhibition of IL-17A	AS, ERA, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection, risankizumab-rzaa IV infusion)	Inhibition of IL-23	SC formulation: CD, PsA, PsO
		IV formulation: CD
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC

* 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.

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Lupus – Benlysta Intravenous Utilization Management Medical 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 medical benefit coverage of Benlysta intravenous. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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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 ≥ 5 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 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).

Dosing. Approve the following dosing regimen (A and B):

A) The dose is up to 10 mg/kg given as an intravenous infusion; AND

B) Doses are administered at Weeks 0, 2, and 4, with subsequent doses separated by at least 4 weeks.

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2. Systemic Lupus Erythematosus. 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 ≥ 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).

Dosing. Approve the following dosing regimen (A and B):
A) The dose is up to 10 mg/kg given as an intravenous infusion; AND
B) Doses are administered at Weeks 0, 2, and 4, with subsequent doses separated by at least 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Benlysta intravenous is not recommended in the following situations:

1. **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 other 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Conditions Not Recommended for Approval:** Concurrent use with Lupkynis (voclosporin capsules) was added as a condition not recommended for approval.	02/09/2022
Selected Revision	**Lupus Nephritis:** To align with the updated labeling, the age of approval was changed from ≥ 18 years of age to ≥ 5 years of age.	08/24/2022
Annual Revision	No criteria changes.	03/08/2023
Selected Revision	**Lupus Nephritis:** For initial therapy, a requirement was added that the patient has biopsy-confirmed lupus nephritis. For initial therapy and a patient currently receiving Benlysta, the requirement that the patient is taking with standard therapy was changed to more generally require that the patient is taking an immunosuppressive regimen. Leflunomide, methotrexate, and/or systemic corticosteroids were added to existing concurrent medication examples. The exception for a patient who is intolerant to standard therapy due to significant toxicity as determined by the prescriber was removed from the policy.	04/26/2023
Selected Revision	**Lupus Nephritis:** For initial therapy, the requirement that the "Patient has autoantibody-positive systemic lupus erythematosus (SLE), defined as positive for antinuclear antibodies (ANA) and/or anti-double-stranded DNA (anti-dsDNA) antibody" was removed from the policy.	07/05/2023

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Benlysta® (belimumab SC injection, IV infusion)	BLyS inhibitor	SLE, lupus nephritis
Saphnelo™ (anifrolumab-fnia IV infusion)	IFN receptor antagonist	SLE
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PsA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx® (secukinumab SC injection)	Inhibition of IL-17A	AS, ERA, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection)	Inhibition of IL-23	PsA, PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC

* 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.

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Lupus – Saphnelo Utilization Management Medical Policy
- Saphnelo® (anifrolumab-fnia intravenous infusion – AstraZeneca)

REVIEW DATE: 08/23/2023

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 medical benefit coverage of Saphnelo. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **Systemic Lupus Erythematosus.** 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.** 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.
- **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 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.

Dosing. Approve 300 mg given as an intravenous infusion administered not more frequently than once every 4 weeks.

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

1. Saphnelo®injection, for intravenous use [prescribing information]. Wilmington DE: AstraZeneca; September 2022.
2. 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/24/2022
Annual Revision	No criteria changes.	08/23/2023

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Saphnelo™ (anifrolumab-fnia IV infusion)	IFN receptor antagonist	SLE
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PsA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx® (secukinumab SC injection)	Inhibition of IL-17A	AS, ERA, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection, risankizumab-rzaa IV infusion)	Inhibition of IL-23	SC formulation: CD, PsA, PsO
		IV formulation: CD
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO, PsA
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC

* 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.

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Metabolic Disorders – Nulibry Utilization Management Medical 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 medical benefit coverage of Nulibry. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 require 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

1. **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.

   Dosing. Approve up to 0.9 mg/kg given by intravenous infusion once daily.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nulibry 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. Nulibry intravenous infusion [prescribing information]. Boston, MA: Origin Biosciences; October 2022.
2. Mechler K, Mountford WK, Hoffmann GF, et al. Ultra-orphan diseases: a quantitative analysis of the natural history of molybdenum cofactor deficiency. *Genet Med*. 2015 Dec;17(12):965-70.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	03/23/2022
Annual Revision	No criteria changes.	03/29/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Migraine – Calcitonin Gene-Related Peptide Inhibitors – Vyepti Utilization Management Medical 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]

The recommended dosage is 100 mg administered by intravenous (IV) infusion over approximately 30 minutes once every 3 months; however, some patients may benefit from a dosage of 300 mg IV once every 3 months.[1] Vyepti must be administered by a healthcare provider.

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 medical benefit coverage of Vyepti. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **Migraine Headache Prevention.** Approve Vyepti 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-preventative 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 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 of another standard prophylactic (preventive) pharmacologic therapy, according to the prescriber; AND

E) 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.

Dosing. Approve up to 300 mg administered by intravenous infusion once every 3 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vyepti is not recommended in the following situations:

1. **Acute Treatment of Migraine.** Clinical data are currently lacking for the use of Vyepti in the acute treatment of migraine.

2. **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]

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 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 injectable CGRP inhibitors and have not been studied for use in combination with another agent in the same class.[1,9-11] 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. 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. Vyepti® injection for intravenous use [prescribing information]. Bothell, WA: Lundbeck; October 2022.
2. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition. *Cephalalgia*. 2018;38:1-211.
3. MacGregor EA. In the clinic. Migraine. *Ann Intern Med*. 2017;166(7):ITC49-ITC64.

4. Lipton RB, Silberstein SD. Episodic and chronic migraine headache: breaking down barriers to optimal treatment and prevention. *Headache*. 2015;52:103-122.
5. American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019;59:1-18.
6. 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;00:1–19.
7. Ashina M, Saper J, Cady R, et al. Eptinezumab in episodic migraine: a randomized, double-blind, placebo-controlled study (PROMISE-1). *Cephalalgia*. 2020;40(3):241-254.
8. Data on file. Eptinezumab-jjmr Pre-Approval Dossier, version 1.7. Lundbeck, Inc.; Deerfield, IL; received on March 2, 2020.
9. Aimovig® injection for subcutaneous use [prescribing information]. Thousand Oaks, CA: Amgen; October 2022.
10. Ajovy® injection for subcutaneous use [prescribing information]. North Wales, PA: Teva; September 2021.
11. Emgality® injection for subcutaneous use [prescribing information]. Indianapolis, IN: Lilly; May 2022.
12. Qulipta® tablets [prescribing information]. Madison, NJ: AbbVie; April 2023.
13. Nurtec® ODT [prescribing information]. New Haven, CT: Biohaven; April 2022.
14. Micromedex. Merative LP. Available at: https://www.micromedexsolutions.com/. Accessed on August 7, 2023. Search terms: lisinopril, verapamil.
15. Clinical Pharmacology. ClinicalKey. Available at: https://www.clinicalkey.com/pharmacology/ Accessed on August 7, 2023. Search terms: lisinopril, verapamil.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Migraine Headache Prevention:** • The criterion requiring a trial of at least one triptan was removed. • The criterion for "Patient is NOT taking a calcitonin gene-related peptide (CGRP) inhibitor for migraine headache prevention" and "Patient is switching from a different CGRP inhibitor for migraine headache prevention to Vyepti" were removed. • The criterion "Patient is currently taking Vyepti and has had a significant clinical benefit from the medication as determined by the prescriber" was changed to "If the patient is currently taking Vyepti, the patient has had a significant clinical benefit from the medication as determined by the prescriber". **Conditions Not Recommended for Approval:** • To add clarity, preventive treatment of migraine with Nurtec ODT was moved into its own criterion that cannot be used concurrently with Vyepti. • The criterion for combination use with Aimovig, Ajovy, Emgality, and Vyepti was changed to read "Concurrent use with another CGRP inhibitor indicated for migraine headache prevention". • Qulipta was added to the Note listing CGRP inhibitors that are indicated for migraine headache prevention.	05/18/2022
Annual Revision	**Policy Name:** The initial descriptor "Migraine" was added to the policy name. **Migraine Headache Prevention:** The note with examples of standard prophylactic (preventive) pharmacologic therapies was expanded to include the statement: Of note, "standard prophylactic (preventive) pharmacologic therapies" do **not** include oral or injectable CGRP inhibitors.	05/24/2023
Selected Revision	**Migraine Headache Prevention:** • The note with standard prophylactic (preventive) pharmacologic therapies was changed to remove "Examples of" and to remove the statement: Of note, "standard prophylactic (preventive) pharmacologic therapies" do **not** include oral or injectable CGRP inhibitors. • A new statement was added to the note: 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.	08/02/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Multiple Sclerosis – Lemtrada Utilization Management Medical Policy
- Lemtrada® (alemtuzumab intravenous infusion – Genzyme)

REVIEW DATE: 11/30/2022

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 has 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 medical benefit coverage of Lemtrada. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 is recommended in those who meet the following criteria:

FDA-Approved Indication

1. Multiple Sclerosis. Approve for the duration noted if the patient meets one of the following (A or B):

A) 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), or Ocrevus (ocrelizumab intravenous infusion); 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
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
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 that specializes in the treatment of multiple sclerosis; OR

B) 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.

Dosing. Approve the following dosing regimens (A or B):

A) First treatment course is 12 mg/day by intravenous infusion on 5 consecutive days (60 mg total dose); OR

B) For additional treatment courses, the dose is 12 mg/day by intravenous infusion on 3 consecutive days (36 mg total dose) administered 12 months after the last Lemtrada treatment course.

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 MS with non-relapsing forms of the disease.[1]
   Note: An example of a non-relapsing form of MS is primary progressive MS.

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. Lemtrada® intravenous infusion [prescribing information]. Cambridge, MA: Genzyme; August 2022.
2. 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 17, 2022.
3. McGinley MP, Goldschmidt C, Rae-Grant AD. Diagnosis and treatment of multiple sclerosis. A review. *JAMA*. 2021;325(8):765-779.
4. No authors listed. Drugs for multiple sclerosis. *Med Lett Drugs Ther*. 2021;63(1620):42-48.
5. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
6. 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.
7. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018;90:777-788.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Wording in the Policy Statement was changed from "All approvals are provided for the duration noted below" to "All approvals are provided for 30 days which is an adequate duration for the patient to receive the recommended number of doses." In addition, the following changes were made: **Multiple Sclerosis:** For initial therapy, the duration of approval was changed from 5 days to five doses. For a patient who has completed a previous Lemtrada therapy course, the duration of approval was changed from 3 days to three doses. For the initial therapy requirement that the patient try two disease-modifying agents used for multiple sclerosis, examples of medications used for multiple sclerosis were changed from a Note to an Appendix and Ponvory was added to the list of examples. Also, the citing of the medication routes were updated, as well as generic availability. Regarding highly aggressive MS, the examples regarding rapidly advancing deterioration in physical functioning and magnetic resonance imaging suggest highly active or aggressive multiple sclerosis were moved from the criteria to a Note. **Conditions Not Recommended for Approval:** Regarding Concurrent Use with Other Disease-Modifying Agents for Multiple Sclerosis, examples provided in the Note were changed to an Appendix and Ponvory was added to the list. Also, the citing of the medication routes were updated, as well as generic availability.	12/08/2021
Selected Revision	**Multiple Sclerosis:** For initial therapy, a patient who has previously received one of Kesimpta, Ocrevus, or Tysabri does not have to meet the requirement for a trial of two other disease-modifying agents for multiple sclerosis. For a patient who has completed a previous Lemtrada therapy course, response criteria were developed for reauthorization in which the patient either experienced a beneficial clinical response when assessed by at least one objective measure (with examples provided in a Note), or the 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.	07/20/2022
Annual Revision	No criteria changes.	11/30/2022

APPENDIX

Medication	Mode of Administration
Aubagio® (teriflunomide tablets)	Oral
Avonex® (interferon beta-1a intramuscular injection)	Injection (self-administered)
Bafiertam® (monomethyl fumarate delayed-release capsules)	Oral
Betaseron® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Copaxone® (glatiramer acetate subcutaneous injection, generic)	Injection (self-administered)
Extavia® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Gilenya® (fingolimod capsules, generic)	Oral
Glatopa® (glatiramer acetate subcutaneous injection)	Injection (self-administered)
Kesimpta® (ofatumumab subcutaneous injection)	Injection (self-administered)
Lemtrada® (alemtuzumab intravenous infusion)	Intravenous infusion
Mavenclad® (cladribine tablets)	Oral
Mayzent® (siponimod tablets)	Oral
Ocrevus® (ocrelizumab intravenous infusion)	Intravenous infusion
Plegridy® (peginterferon beta-1a subcutaneous or intramuscular injection)	Injection (self-administered)
Ponvory™ (ponesimod tablets)	Oral
Rebif® (interferon beta-1a subcutaneous injection)	Injection (self-administered)
Tecfidera® (dimethyl fumarate delayed-release capsules, generic)	Oral
Tysabri® (natalizumab intravenous infusion)	Intravenous infusion
Vumerity® (diroximel fumarate delayed-release capsules)	Oral
Zeposia® (ozanimod capsules)	Oral

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Multiple Sclerosis – Ocrevus Utilization Management Medical Policy
- Ocrevus® (ocrelizumab intravenous infusion – Biogen)

REVIEW DATE: 11/30/2022; selected revision 03/01/2023

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 medical benefit coverage of Ocrevus. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **Multiple Sclerosis, Relapsing Forms.** 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 the following (i, ii, and iii):
     - **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 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 Ocrevus for ≥ 1 Year. Approve if the patient meets all of the following (i, ii, iii, and iv):
     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).
     - **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 [(1) or (2)]:
       - **(1)** 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.
       - **(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 physician who specializes in the treatment of multiple sclerosis.

   Dosing. Approve the following dosing regimens (A or B):
   - **A)** 300 mg by intravenous infusion, followed 2 weeks later by a second 300 mg intravenous infusion; OR
   - **B)** 600 mg by intravenous infusion once every 6 months.

2. **Multiple Sclerosis, Primary Progressive.** Approve for 1 year if the patients meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Ocrevus is prescribed by or in consultation with a physician who specializes in the treatment of multiple sclerosis and/or a neurologist.

   Dosing. Approve the following dosing regimens (A or B):
   A) 300 mg by intravenous infusion, followed 2 weeks later by a second 300 mg intravenous infusion; OR
   B) 600 mg by intravenous infusion once every 6 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ocrevus is not recommended in the following situations:

1. **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.

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. Ocrevus® intravenous infusion [prescribing information]. San Francisco, CA: Genentech/Roche; August 2022.
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 17, 2022.
3. McGinley MP, Goldschmidt C, Rae-Grant AD. Diagnosis and treatment of multiple sclerosis. A review. *JAMA*. 2021;325(8):765-779.
4. The Medical Letter on Drugs and Therapeutics. Drugs for multiple sclerosis. *Med Lett Drugs Ther*. 2021;63(1620):42-48.
5. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
6. 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Conditions Not Recommended for Approval:** Regarding Concurrent Use with Other Disease-Modifying Agents for Multiple Sclerosis, examples provided in the Note were changed to an Appendix table and Ponvory was added to the list. Also, the citing of the medication routes were updated, as well as generic availability.	12/08/2021
Selected Revision	**Multiple Sclerosis, Relapsing Forms:** Criteria were divided into Initial Therapy and Patient Has Been Receiving Ocrevus for < 1 year and for 1 year or more. For Initial Therapy, criteria were added that according to the prescriber the patient has experienced inadequate efficacy or significant intolerance to one disease-modifying agent used for multiple sclerosis (with a Note added that the Appendix provides examples). For those receiving Ocrevus for 1 year or more, response criteria were developed for reauthorization in which the patient either experienced a beneficial clinical response when assessed by at least one objective measure (with examples provided in a Note), or the 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.	07/20/2022
Annual Revision	No criteria changes.	11/30/2022
Selected Revision	**Multiple Sclerosis. Relapsing Forms:** For initial criteria, the criterion was removed that according to the prescriber, the patient has experienced inadequate efficacy or significant intolerance to one disease-modifying agent used for multiple sclerosis. The criteria regarding use of Ocrevus for < 1 year was deleted as now it is the same as initial criteria. For the criteria regarding the patient is currently receiving Ocrevus for 1 year or more, a Note was added stating that a patient who has received < 1 year of therapy or who is restarting therapy with Ocrevus should be considered under criteria for Multiple Sclerosis (Relapsing Forms) [Initial Therapy]. **Conditions Not Recommended for Approval:** Regarding Concurrent Use with Other Disease-Modifying Agents for Multiple Sclerosis, Briumvi was added to the list of examples provided in the Appendix table.	03/01/2023

APPENDIX

Medication	Mode of Administration
Aubagio® (teriflunomide tablets)	Oral
Avonex® (interferon beta-1a intramuscular injection)	Injection (self-administered)
Bafiertam® (monomethyl fumarate delayed-release capsules)	Oral
Betaseron® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Briumvi™ (ublituximab-xiiy intravenous infusion)	Intravenous infusion
Copaxone® (glatiramer acetate subcutaneous injection, generic)	Injection (self-administered)
Extavia® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Gilenya® (fingolimod capsules, generic)	Oral
Glatopa® (glatiramer acetate subcutaneous injection)	Injection (self-administered)
Kesimpta® (ofatumumab subcutaneous injection)	Injection (self-administered)
Lemtrada® (alemtuzumab intravenous infusion)	Intravenous infusion
Mavenclad® (cladribine tablets)	Oral
Mayzent® (siponimod tablets)	Oral
Ocrevus® (ocrelizumab intravenous infusion)	Intravenous infusion
Plegridy® (peginterferon beta-1a subcutaneous or intramuscular injection)	Injection (self-administered)
Ponvory™ (ponesimod tablets)	Oral
Rebif® (interferon beta-1a subcutaneous injection)	Injection (self-administered)
Tascenso ODT™ (fingolimod orally disintegrating tablets)	Oral
Tysabri® (natalizumab intravenous infusion)	Intravenous infusion
Vumerity® (diroximel fumarate delayed-release capsules)	Oral
Zeposia® (ozanimod capsules)	Oral

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Multiple Sclerosis and Crohn's Disease – Tysabri Utilization Management Medical Policy
- Tysabri® (natalizumab intravenous infusion – Biogen)

REVIEW DATE: 11/30/2022

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.[2-4] 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.

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.[8,9] 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 inhibitors or who have had no prior exposure to anti-TNF inhibitors.

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 medical benefit coverage of Tysabri. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 multiple sclerosis 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 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 all of 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)]:
         - **(1)** Patient has demonstrated rapidly advancing deterioration(s) in physical functioning **[documentation required]**; OR
           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
           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
   - **B)** Patient is Currently Receiving Tysabri. Approve if the patient meets one of the following criteria (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 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)]:
  - **(1)** 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.
  - **(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
- **d)** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

Dosing. Approve up to 300 mg given by intravenous infusion administered no more frequently than once every 4 weeks.

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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 product (Remicade, biosimilars), Entyvio (vedolizumab intravenous infusion), Skyrizi (risankizumab-rzaa intravenous infusion, risankizumab-rzaa subcutaneous injection [on-body injector]), or Stelara (ustekinzumab subcutaneous injection or intravenous infusion).
  Note: Each biosimilar tried from the same chemical would only count as a trial of one product.
- **iv.** Tysabri 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 criteria 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
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 tomograph 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

iv. Medication is prescribed by or in consultation with a gastroenterologist.

Dosing in Crohn's Disease. Approve up to 300 mg given by intravenous infusion administered no more frequently than once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tysabri is not recommended in the following situations:

1. **Concurrent Use with an Immunosuppressant Agent in Patients 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]
   Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, methotrexate, an infliximab product, an adalimumab product, Cimzia, Entyvio, Skyrizi (risankizumab-rzaa intravenous infusion, risankizumab-rzaa subcutaneous injection [on-body injector]), and Stelara.

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.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Multiple Sclerosis:** For the initial therapy requirement that the patient try one disease-modifying agent used for multiple sclerosis, examples of medications used for multiple sclerosis were changed from a Note to an Appendix and Ponvory was added to the list of examples. Also, the citing of the medication routes were updated, as well as generic availability. Regarding highly aggressive multiple sclerosis, the examples regarding rapidly advancing deterioration in physical functioning and magnetic resonance imaging suggest highly active or aggressive multiple sclerosis were moved from the criteria to a Note. **Conditions Not Recommended for Approval:** Regarding Concurrent Use with Other Disease-Modifying Agents for Multiple Sclerosis, examples provided in the Note were changed to an Appendix and Ponvory was added to the list. Also, the citing of the medication routes were updated, as well as generic availability.	12/08/2021
Selected Revision	**Multiple Sclerosis:** For patients currently receiving therapy, the criteria were divided among patients receiving therapy for < 1 year and those receiving Tysabri for 1 year or more. For a patient receiving Tysabri for 1 year or more, response criteria were developed for reauthorization in which the patient either experienced a beneficial clinical response when assessed by at least one objective measure (with examples provided in a Note), or the 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. For the specialist requirement, the criteria was changed from "prescribed by or in consultation with a physician who specializes in the treatment of multiple sclerosis and/or a neurologist" to "prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis." **Crohn's Disease:** The Note which contains a list of biologics for use in Crohn's Disease was updated to now include Skyrizi (risankizumab-rzaa intravenous infusion, risankizumab-rzaa subcutaneous injection [on-body injector]).	07/20/2022
Selected Revision	**Crohn's Disease:** The duration of initial therapy was changed from 3 months to 6 months. To the Note that has a list of medication examples, the statement was added that a previous trial of the requested biologic (or a biosimilar of the requested biologic) does not count. For a patient currently receiving criteria, it was added as a criterion that the patient has been established on therapy for at least 6 months. A Note was also added that for a patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy). Criteria were also added in this section that a patient has experienced a beneficial clinical response from baseline (prior to initiating Tysabri) by at least one objective measure (with examples provided in the criteria as a note) or 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. The previous criteria and Note that asked if the patient has had a response as determined by the prescriber were removed (replaced with the criteria above). **Conditions Not Recommended for Approval:** To the clinical situation of Concurrent Use with an Immunosuppressant Agent in Patients with Crohn's Disease, Skyrizi (risankizumab-rzaa intravenous infusion, risankizumab-rzaa subcutaneous injection [on-body injector]) was added to the Note that lists the medications that should not be used concomitantly.	07/27/2022
Annual Revision	No criteria changes.	11/23/2022

APPENDIX

Medication	Mode of Administration
Aubagio® (teriflunomide tablets)	Oral
Avonex® (interferon beta-1a intramuscular injection)	Injection (self-administered)
Bafiertam® (monomethyl fumarate delayed-release capsules)	Oral
Betaseron® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Copaxone® (glatiramer acetate subcutaneous injection, generic)	Injection (self-administered)
Extavia® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Gilenya® (fingolimod capsules, generic)	Oral
Glatopa® (glatiramer acetate subcutaneous injection)	Injection (self-administered)
Kesimpta® (ofatumumab subcutaneous injection)	Injection (self-administered)
Lemtrada® (alemtuzumab intravenous infusion)	Intravenous infusion
Mavenclad® (cladribine tablets)	Oral
Mayzent® (siponimod tablets)	Oral
Ocrevus® (ocrelizumab intravenous infusion)	Intravenous infusion
Plegridy® (peginterferon beta-1a subcutaneous or intramuscular injection)	Injection (self-administered)
Ponvory® (ponesimod tablets)	Oral
Rebif® (interferon beta-1a subcutaneous injection)	Injection (self-administered)
Tecfidera® (dimethyl fumarate delayed-release capsules, generic)	Oral
Tysabri® (natalizumab intravenous infusion)	Intravenous infusion
Vumerity® (diroximel fumarate delayed-release capsules)	Oral
Zeposia® (ozanimod capsules)	Oral

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Muscular Dystrophy – Exondys 51 Utilization Management Medical 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

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] 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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/27/2022
Update	08/12/2022: A summary of the shortcomings of clinical data with Exondys 51 were added to the denial rationale.	NA
Annual Revision	No criteria changes.	04/26/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Muscular Dystrophy – Gene Therapy – Elevidys Utilization Management Medical 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.

Dosing

The recommended dose is 1.33 x 10^{14} vg/kg of body weight (or 10 mL/kg body weight).[1] Immune responses to the AAVrh74 vector can occur after Elevidys administration. To reduce this risk, corticosteroids should be administered starting one day prior to Elevidys infusion and continued for a minimum of 60 days after the infusion, unless earlier tapering is clinically indicated.

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:

1. **Duchenne Muscular Dystrophy (DMD).** Approval is not recommended due to the unclear clinical benefit of Elevidys. 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.

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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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/19/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Muscular Dystrophy – Viltepso Utilization Management Medical 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.

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 systematic 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 history 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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/24/2022
Annual Revision	No criteria changes	08/30/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Muscular Dystrophy – Vyondys 53 Utilization Management Medical Policy
- Vyondys 53™ (golodirsen intravenous infusion – Sarepta)

REVIEW DATE: 12/07/2022

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 in the guidelines.

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:

1. **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 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 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 trial to verify clinical efficacy of Vyondys 53.

   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 history 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).

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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	12/15/2021
Update	08/12/2022: A summary of the shortcomings of clinical data with Vyondys 53 were added to the denial rationale.	NA
Annual Revision	No criteria changes.	12/07/2022

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Neurology – Gene Therapy – Skysona Utilization Management Medical Policy
- Skysona® (elivaldogene autotemcel intravenous infusion – Bluebird Bio)

REVIEW DATE: 11/02/2022

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 treatment of 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 benefit coverage of Skysona. Approval is recommended for those who meet the **Criteria** and **Dosing** 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 administered one dose of therapy. For certain criteria, attestation is required as noted by **[attestation required by physician]**. 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

1. **Cerebral Adrenoleukodystrophy.** Approve a one-time (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, Q, R, and S).
   - **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 as determined by the prescribing physician; 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; OR
     - **ii.** Estimated glomerular filtration rate is ≥ 70 mL/minute/1.73 m^2; 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 plans to 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) Medication is prescribed by a hematologist, a neurologist, and/or a stem cell transplant specialist.

* Refer to the Policy Statement.

Dosing. The single dose is given intravenously which contains a minimum of 5.0×10^6 CD34+ cells/kg of body weight in which body weight is based on patient weight prior to first apheresis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Skysona is not recommended in the following situations:

1. **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.

2. **Prior Hematopoietic Stem Cell Transplantation [attestation required by physician]**. Allogeneic transplant was an exclusion criterion in the pivotal studies.

3. **Prior Receipt of Gene Therapy**. This was an exclusion criterion in the pivotal studies.

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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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	11/02/2022

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Neurology – Qalsody Utilization Management Medical 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 is not recommended in the following situations:

1. **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.

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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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	05/24/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Neurology – Radicava Intravenous Utilization Management Medical Policy
- Radicava® (edaravone intravenous infusion – Mitsubishi Tanabe)

REVIEW DATE: 04/19/2023

OVERVIEW

Radicava intravenous (IV) is indicated for the treatment of **amyotrophic lateral sclerosis** (ALS).[1]

Radicava IV is an anti-oxidative, free radical scavenger which eliminates lipid peroxide and hydroxyl radicals; however, it is unknown exactly how Radicava IV exerts its therapeutic effect in ALS.[1-2]

Of note, Radicava ORS® (edaravone oral suspension) is indicated for the treatment of ALS.[14] Radicava ORS received FDA-approval under the 505(b)(2) approval pathway which relied upon evaluations of safety and efficacy for Radicava IV. Patients treated with Radicava IV may be switched to Radicava ORS using the same dosing frequency.

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]

Guidelines

The American Academy of Neurology practice parameter on the care of patients with ALS (last updated 2009; reaffirmed 2023) does not yet address Radicava IV.[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 medical benefit coverage of Radicava IV. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 as well as the monitoring required for adverse events and long-term efficacy, approval requires Radicava IV 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 is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. 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.

Dosing. Approve the following dosing regimens (A and B):

A) 60 mg intravenous infusion once daily; AND

B) Treatment Cycles:
- **i.** Initial Cycle: Administer for 14 days followed by a 14-day drug-free period.
- **ii.** Subsequent cycles: Administer for 10 days out of a 14-day period, followed by a 14-day drug-free period.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Radicava IV is not recommended in the following situations:

1. **Aneurysmal Subarachnoid Hemorrhage.** Radicava IV is not indicated for the treatment of aneurysmal subarachnoid hemorrhage (SAH).[1] 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.

2. **Myocardial Infarction.** Radicava IV is not indicated for the treatment of myocardial infraction; there are no US or North American studies of Radicava IV for this indication.[1] 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).

3. **Radiation-Induced Brain Injury.** Radicava IV is not indicated for the treatment of radiation-induced brain injury; there are no US or North American studies of Radicava IV for this indication.[1] 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.

4. **Retinal Vein Occlusion.** Radicava IV is 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 for this indication.[1] 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.

5. **Sensorineural Hearing Loss.** Radicava IV is not indicated for the treatment of sensorineural hearing loss; there are no US-based studies of Radicava IV for this indication.[1] 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.

6. **Stroke.** Radicava IV is not FDA-approved for the treatment of patients who have experienced stroke.[1] 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.

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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	03/23/2022
Selected Revision	**Amyotrophic Lateral Sclerosis (ALS):** For a patient currently receiving the medication, Radicava ORS was added as an option.	06/01/2022
Annual Revision	No criteria changes.	04/19/2023

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 history or examination.

Together with the absence of:

- Electrophysiological or pathological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration; AND
- 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.**

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Neurology – Rystiggo Utilization Management Medical 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 improvements in the secondary efficacy endpoints were also observed in the Rystiggo groups vs. placebo.

Dosing Information

Rystiggo is administered as a subcutaneous (SC) infusion, at a rate of up to 20 mL/h; infusions are given once weekly by a healthcare professional.[1] For patients weighing < 50 kg, the recommended dose is 420 mg; for patients 50 kg to < 100 kg, the recommended dose is 560 mg; and for patients ≥ 100 kg, the recommended dose is 840 mg. Each treatment cycle is 6 injections (6 weeks). Administer subsequent treatment cycles based on clinical evaluation. The safety of initiating subsequent cycles sooner than 63 days from the start of the previous treatment cycle has not been established.

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 medical benefit coverage of Rystiggo. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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i. Generalized Myasthenia Gravis. Approve 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, vi, and vii):

i. Patient is ≥ 18 years of age; AND

ii. 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

iii. Patient meets both of the following (a and b):

a) Myasthenia Gravis Foundation of America class of II to IV; AND

b) Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 3 for non-ocular symptoms; 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 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 63 days from the start of the previous treatment cycle; AND

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

B) 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.

Dosing. Approve the following dosing regimens (A or B):
A) Patient < 50 kg. The dose is 420 administered by subcutaneous infusion once weekly for 6 weeks; OR
B) Patient is 50 kg to < 100 kg. The dose is 560 administered by subcutaneous infusion once weekly for 6 weeks; OR
C) Patient ≥ 100 kg. The dose is 840 administered by subcutaneous infusion once weekly for 6 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rystiggo is not recommended in the following situations:

1. **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.
Note: Examples of neonatal Fc receptor blockers are Vyvgart (efgartigimod alfa-fcab intravenous infusion] and Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection).
Note: Examples of complement inhibitors are Soliris (eculizumab intravenous infusion), Ultomiris (ravulizumab-cwvz intravenous infusion or subcutaneous injection), and Zilbrysq (zilucoplan subcutaneous injection).

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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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/05/2023
Selected Revision	**Conditions Not Recommended for Approval:** Added "Concomitant Use with Another Neonatal Fc Receptor Blocker, a Complement Inhibitor, or a Rituximab Product". Examples of Neonatal Fc Receptor Blockers and Complement Inhibitors are listed as Notes.	10/18/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Neurology – Vyvgart Hytrulo Utilization Management Medical Policy
- Vyvgart® Hytrulo (efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection – Argenx/Halozyme)

REVIEW DATE: 07/05/2023; selected revision 10/18/2023

OVERVIEW

Vyvgart Hytrulo, a neonatal Fc receptor blocker, is indicated for the treatment of **generalized myasthenia gravis** in adults who are anti-acetylcholine receptor antibody positive.

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).

Dosing Information

The recommended dose is one vial (1,008 mg efgartigimod alfa and 11,200 units hyaluronidase) administered as a subcutaneous injection over 30 to 90 sections once weekly.[1] Each treatment cycle is four injections (4 weeks). Administer subsequent treatment cycles based on clinical evaluation. The safety of

initiating subsequent cycles sooner than 50 days from the start of the previous treatment cycle has not been established. Vyvgart Hytrulo should be administered by a healthcare professional.

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 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 medical benefit coverage of Vyvgart Hytrulo. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 Hytrulo as well as the monitoring required for adverse events and long-term efficacy, approval requires Vyvgart 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

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1. **Generalized Myasthenia Gravis.** Approve 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, 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 ≥ 5; 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 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); AND

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.

B) 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.

Dosing. Approve the following dosing regimen:

A) One vial (1,008 mg efgartigimod alfa and 11,200 units hyaluronidase) administered as a subcutaneous injection once weekly for 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vyvgart Hytrulo is not recommended in the following situations:

1. **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.
   Note: Examples of neonatal Fc receptor blockers are Rystiggo (rozanolixizumab-noli subcutaneous infusion) and Vyvgart (efgartigimod alfa-fcab intravenous infusion).
   Note: Examples of complement inhibitors are Soliris (eculizumab intravenous infusion), Ultomiris (ravulizumab-cwvz intravenous infusion or subcutaneous injection), and Zilbrysq (zilucoplan subcutaneous injection).

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. Vyvgart® Hytrulo subcutaneous injection. Boston, MA and San Diego, CA: Argenx and Halozyme; June 2023.
2. National Institute of Neurological Disorders and Stroke (NINDS). Myasthenia Gravis Fact Sheet. National Institutes of Health (NIH) Publication No. 17-768. Publication last updated: March 2020. Available at: https://www.ninds.nih.gov/sites/default/files/migrate-documents/myasthenia_gravis_e_march_2020_508c.pdf Accessed on June 12, 2023.
3. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. *Neurology*. 2016;87:419–425.
4. Data on File. ADAPT-SC – Argenx. Received June 13, 2023.
5. Vyvgart® intravenous infusion [prescribing information]. Boston, MA: Argenx; May 2022.
6. Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. *Neurology*. 2021;96(3):114-122.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/05/2023
Selected Revision	**Conditions Not Recommended for Approval:** Added "Concomitant Use with Another Neonatal Fc Receptor Blocker, a Complement Inhibitor, or a Rituximab Product". Examples of neonatal Fc receptor blockers and complement inhibitors were listed as Notes.	10/18/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Neurology – Vyvgart Intravenous Utilization Management Medical 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]

Dosing Information

For patients weighing < 120 kg, the recommended dose is 10 mg/kg administered as an intravenous infusion over one hour once weekly for 4 weeks.[1] For patients weighing ≥ 120 kg, the recommended dose is 1200

mg per infusion. Administer subsequent treatment cycles based on clinical evaluation. The safety of initiating subsequent cycles sooner than 50 days from the start of the previous treatment cycle has not been established.

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 medical benefit coverage of Vyvgart Intravenous. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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1. Generalized Myasthenia Gravis. Approve 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, 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 ≥ 5; 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 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); AND

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.

B) 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.

iv. Treatment cycles are no more frequent than every 50 days from the start of the previous treatment cycle; AND

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

Dosing. Approve one of the following dosing regimens (A or B):

A) Patient < 120 kg. The dose is 10 mg/kg administered by intravenous infusion once weekly for 4 weeks; OR

B) Patient ≥ 120 kg. The dose is 1200 mg administered by intravenous infusion once weekly for 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vyvgart Intravenous is not recommended in the following situations:

1. **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.
   Note: Examples of neonatal Fc receptor blockers are Rystiggo (rozanolixizumab-noli subcutaneous infusion) and Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc subcutaneous injection).
   Note: Examples of complement inhibitors are Soliris (eculizumab intravenous infusion), Ultomiris (ravulizumab-cwvz intravenou infusion or subcutaneous injection), and Zilbrysq (zilucoplan subcutaneous injection).

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. Vyvgart® intravenous infusion [prescribing information]. Boston, MA: Argenx; May 2022.
2. National Institute of Neurological Disorders and Stroke (NINDS). Myasthenia Gravis Fact Sheet. National Institutes of Health (NIH) Publication No. 17-768. Publication last updated: March 2020. Available at: https://www.ninds.nih.gov/sites/default/files/migrate-documents/myasthenia_gravis_e_march_2020_508c.pdf Accessed on June 12, 2023.
3. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. *Neurology*. 2016;87:419–425.
4. Vyvgart® Hytrulo subcutaneous injection. Boston, MA and San Diego, CA: Argenx and Halozyme; June 2023.
5. Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. *Neurology*. 2021 Jan 19;96(3):114-122.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Generalized Myasthenia Gravis:** A requirement for treatment cycles to be no more frequent than every 50 days from the start of the previous cycle was added to criteria. The frequency for cycles was removed from the dosing section.	11/16/2022
Early Annual Revision	**Generalized Myasthenia Gravis,** Criteria for "Patient is Currently Receiving Vyvgart": Added Vyvgart Hytrulo to the criterion as the criteria will apply to a patient who is currently receiving Vyvgart or Vyvgart Hytrulo. Criterion "Patient is continuing to derive benefit from Vyvgart, according to the prescriber": Added Vyvgart Hytrulo. Criterion regarding evidence of unresolved symptoms of generalized myasthenia gravis: examples are moved to a Note. Policy renamed from Neurology – Vyvgart to Neurology – Vyvgart Intravenous.	07/05/2023
Selected Revision	**Conditions Not Recommended for Approval:** Added "Concomitant Use with Another Neonatal Fc Receptor Blocker, a Complement Inhibitor, or a Rituximab Product". Examples of Neonatal Fc Receptor Blockers and Complement Inhibitors are listed as Notes.	10/18/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Ophthalmology – Durysta Utilization Management Medical Policy
- Durysta® (bimatoprost implant, for intracameral administration – Allergan)

REVIEW DATE: 04/27/2022

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 medical benefit coverage of Durysta. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 Zioptan (tafluprost 0.0015% 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.

   Dosing. Approve up to one Durysta implant per treated eye(s) [two implants per patient].

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), and Zioptan (tafluprost 0.0015% 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.

Dosing. Approve up to one Durysta implant per treated eye(s) [two implants per patient].

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Durysta is not recommended in the following situations:

1. **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.

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. Durysta® [prescribing information]. Madison, NJ: Allergan; November 2020.
2. Boyd K. Glaucoma. Available at: https://www.aao.org/eye-health/diseases/what-is-glaucoma. Accessed on April 15, 2022.
3. 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 15, 2022.
4. Facts and Comparisons® Online. Wolters Kluwer Health, Inc.; 2022. Available at: http://online.factsandcomparisons.com/login.aspx?url=/index.aspx&qs=. Accessed on April 15, 2022. Search terms: ophthalmic beta blockers, alpha agonists, prostaglandins, netarsudil.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/21/2021
Annual Revision	The indication "Reduction of Intraocular Pressure (IOP) in Patients with Open-Angle Glaucoma or Ocular Hypertension" was separated into two indications for approval: Ocular Hypertension and Open-angle glaucoma. The criteria for approval were not changed.	04/27/2022

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Ophthalmology – Gene Therapy – Luxturna Utilization Management Medical 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 fewer than 6 days apart.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Luxturna. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Because of the specialized skills required for evaluation and diagnosis of patients 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 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. 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:

1. **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.

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. Luxturna® subretinal injection [prescribing information]. Philadelphia, PA: Spark Therapeutics; May 2022.
2. 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	02/23/2022
Annual Revision	**Policy Name Change:** The designation "Gene Therapy" was added to the policy title: Ophthalmology – Gene Therapy – Luxturna UM Medical Policy. No criteria changes.	02/22/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Ophthalmology – Izervay Utilization Management Medical 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] The recommended dose for Izervay is 2 mg administered by intravitreal injection to each affected eye once a month (approximately every 28 ± 7 days) for up to 12 months.

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 medical benefit coverage of Izervay. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **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.

Dosing. Approve if the dose meets both criteria (A and B):

A) The dose is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection for each eye being treated; AND

B) The dosing interval is not more frequent than once every 21 days for each eye being treated.
Note: The dosing interval is once monthly (approximately every 28 ± 7 days).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Izervay 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. Izervay™ intravitreal injection [prescribing information]. Parsippany, NJ: Iveric; August 2023.
2. 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.
3. 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.
4. 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.
5. 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.
6. Fleckenstein M, Mitchel P, Freud KB, et al. The progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2018;125:369-390.
7. 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.
8. Data on file. Izervay – GATHER2 study. Iveric; received on August 7, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/16/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Ophthalmology – Syfovre Utilization Management Medical 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] The recommended dose for Syfovre is 15 mg (0.1 mL of 150 mg/mL solution) administered by intravitreal injection to each affected eye once every 25 to 60 days.

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 medical benefit coverage of Syfovre. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **Geographic Atrophy.** Approve for 1 year if the patient meets the following criteria (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) 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.
   - **C)** The medication is administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both criteria (A and B):

A) The dose is 15 mg (0.1 mL of 150 mg/mL solution) administered by intravitreal injection for each eye being treated; AND

B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Syfovre 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. Syfovre™ intravitreal injection [prescribing information]. Waltham, MA: Apellis; February 2023.
2. 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.
3. 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.
4. 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 February 21, 2023.
5. Fleckenstein M, Mitchel P, Freud KB, et al. The progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2018;125:369-390.
6. 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	03/01/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Ophthalmology – Tepezza Utilization Management Medical 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 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 medical benefit coverage of Tepezza. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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1. **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.

   Dosing. Approve up to 20 mg/kg per dose administered by intravenous infusion no more frequently than every 3 weeks for 8 doses.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tepezza 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. Tepezza intravenous infusion [prescribing information]. Lake Forest, IL: Horizon; April 2023.
2. 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 April 20, 2023.
3. Horizon Therapeutics, 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 April 20, 2023.
4. Horizon Therapeutics. Teprotumumab for injection. Briefing document for the Food and Drug Administration Dermatologic and Ophthalmic Drugs Advisory Committee. Meeting Date: December 13, 2019. Available at: https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-public-participation-information-december-13-2019-meeting-dermatologic-and-ophthalmic-drugs#event-information. Accessed on January 10, 2023.
5. Bartley GB, Fatourechi V, Kadrmas EF, et al. Clinical features of Graves' ophthalmopathy in an incidence cohort. *Am J Ophthalmol.* 1996;121(3):284-290.
6. Shan S, Douglas R. The pathophysiology of thyroid eye disease. *J Neuroophthalmol*. 2014 Jun;34(2):177-85.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	01/19/2022
Selected Revision	**Thyroid Eye Disease:** Criteria were removed that allow Tepezza to treat each affected eye. Additionally, examples of active disease of at least moderate severity were moved to a Note.	05/25/2022
Annual Revision	No criteria changes.	01/18/2023
Update	05/24/2023: Tepezza prescribing information was revised in April 2023. FDA-approved indication was revised to "Treatment of thyroid eye disease, regardless of thyroid eye disease or duration" from "Treatment of thyroid eye disease". Criteria were not changed.	--

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Beovu Utilization Management Medical Policy

- Beovu® (brolucizumab intravitreal injection – Novartis)

REVIEW DATE: 11/16/2022

OVERVIEW

Beovu, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the following uses:[1]

- **Diabetic macular edema** (DME).
- **Neovascular (wet) age-related macular degeneration** (nAMD).

For DME, the recommended dose for Beovu is 6 mg administered by intravitreal (IVT) injection every six weeks (every 39 to 45 days) for the first 5 doses, followed by 6 mg IVT injection once every 8 to 12 weeks. For nAMD, the recommended dose for Beovu is 6 mg administered by IVT injection every month (every 25 to 31 days) for the first 3 doses, followed by 6 mg IVT injection once every 8 to 12 weeks.

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 also have the potential to be used off-label and reduce vision loss associated with other eye conditions related to increased VEGF production. 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.[4,5] Anti-VEGF therapy has the potential to be used off-label in other neovascular conditions affecting the eye and may prevent or slow visual impairment.[2,4,5]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Beovu. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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.

Dosing. Approve if the requested dosing meets the following (A and B):
A) The dose is 6 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 39 days for five doses, followed by not more frequently than once every 8 weeks for each eye being treated.

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2. Neovascular (Wet) Age-Related Macular Degeneration. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the requested dosing meets the following (A and B):
A) The dose is 6 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 25 days for three doses, followed by not more frequently than once every 8 weeks for each eye being treated.

Other Uses with Supportive Evidence

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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.

Dosing. Approve if the requested dosing meets the following (A and B):
A) The dose is 6 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 25 days for three doses, followed by not more frequently than once every 8 weeks for each eye being treated.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Beovu 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. Beovu® intravitreal injection [prescribing information]. Hanover, NJ: Novartis; May 2022.
2. Barakat MR, Kaiser PK. VEGF inhibitors for the treatment of neovascular age-related macular degeneration. *Expert Opin Investig Drugs.* 2009;18(5):637-646.
3. Tolentino M. Systemic and ocular safety of intravitreal anti-VEGF therapies for ocular neovascular disease. *Surv Ophthalmol*. 2011;56(2):95-113.
4. Kinnunen K, Ylä-Herttuala S. Vascular endothelial growth factors in retinal and choroidal neovascular diseases. *Ann Med*. 2012;44(1):1-17.
5. Horsley MB, Kahook MY. Anti-VEGF therapy for glaucoma. *Curr Opin Ophthalmol*. 2010;21(2):112-117.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Neovascular (Wet) Age-Related Macular Degeneration:** To align with the FDA-approved dosing, the dose was changed from "≤ 6 mg" to "is 6 mg". **Other Neovascular Diseases of the Eye:** Examples of other neovascular diseases of the eye were moved to a Note. To align with the FDA-approved dosing, the dose was changed from "≤ 6 mg" to "is 6 mg".	11/10/2021
Selected Revision	**Diabetic Macular Edema:** This indication and associated criteria were added to the policy.	06/08/2022
Annual Revision	No criteria changes.	11/16/2022

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Eylea and Eylea HD Utilization Management Medical Policy
- Eylea® (aflibercept intravitreal injection – Regeneron)
- Eylea® HD (aflibercept intravitreal injection – Regeneron)

REVIEW DATE: 11/16/2022; selected revision 02/22/2023 and 08/30/2023

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**.

For all of the indications, except retinopathy of prematurity, the recommended dose for Eylea is 2 mg administered by intravitreal injection. Frequency of the dose varies depending on the condition, although all conditions state some patients may need upper limit dosing of once every 4 weeks (approximately every 25 days, monthly). The dose for retinopathy of prematurity is 0.4 mg administered by intravitreal injection; repeat injections may be given and the treatment interval between doses injected into the same eye should be at least 10 days.

For all indications, the recommended dose for Eylea HD is 8mg administered by intravitreal injection.[6] For diabetic macular edema and neovascular (wet) age-related macular degeneration, the dosing regimen for Eylea HD is every 4 weeks (approximately every 28 days +/- 7 day) for the first three doses, followed by one dose every 8 to 16 weeks, +/- 1 week. For diabetic retinopathy, the dosing is every 4 weeks (approximately every 28 days +/- 7 day) for the first three doses, followed by one dose every 8 to 12 weeks, +/- 1 week.

Other Uses with Supportive Evidence for Eylea

Overproduction of VEGF may lead to other eye conditions, including neovascular glaucoma and other retinal and choroidal neovascular conditions affecting the eye.[2,3] Thus, the VEGF inhibitors have the potential to be used off-label for the treatment of other neovascular diseases of the eye to prevent or reduce vision loss .[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.[4,5]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Eylea and Eylea HD. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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1. Diabetic Macular Edema. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both of the following (A and B):
A) The dose is 2 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

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2. Diabetic Retinopathy. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both of the following (A and B):
A) The dose is 2 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

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3. Macular Edema Following Retinal Vein Occlusion. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both of the following (A and B):
A) The dose is 2 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

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4. Neovascular (Wet) Age-Related Macular Degeneration. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both of the following (A and B):
A) The dose is 2 mg administered by intravitreal injection for each eye being treated; AND

B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

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5. Retinopathy of Prematurity. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both of the following (A and B):
A) The dose is 0.4 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 10 days for each eye being treated.

Other Uses with Supportive Evidence

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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, sickle cell neovascularization, and choroidal neovascular conditions.

Dosing. Approve if the dose meets both of the following (A and B):
A) The dose is 2 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

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

FDA-Approved Indications

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1. Diabetic Macular Edema. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both of the following (A and B):
A) The dose is 8 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 21 days for three doses, followed by not more frequent than once every 7 weeks for each eye being treated.
Note: The recommended dose is once every 4 weeks (approximately every 28 days +/- 7 day) for the first three doses, followed by one dose every 8 to 16 weeks, +/- 1 week.

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2. Diabetic Retinopathy. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both of the following (A and B):
A) The dose is 8 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 21 days for three doses, followed by not more frequent than once every 7 weeks for each eye being treated.
Note: The recommended dose is once every 4 weeks (approximately every 28 days +/- 7 day) for the first three doses, followed by one dose every 8 to 12 weeks, +/- 1 week.

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3. Neovascular (Wet) Age-Related Macular Degeneration. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both of the following (A and B):
A) The dose is 8 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 21 days for three doses, followed by not more frequent than once every 7 weeks for each eye being treated.
Note: The recommended dose is once every 4 weeks (approximately every 28 days +/- 7 day) for the first three doses, followed by one dose every 8 to 16 weeks, +/- 1 week.

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

1. Eylea® intravitreal injection [prescribing information]. Tarrytown, NY: Regeneron; February 2023.
2. Barakat MR, Kaiser PK. VEGF inhibitors for the treatment of neovascular age-related macular degeneration. *Expert Opin Investig Drugs.* 2009;18(5):637-646.
3. Tolentino M. Systemic and ocular safety of intravitreal anti-VEGF therapies for ocular neovascular disease. *Surv Ophthalmol.* 2011;56(2):95-113.
4. Kinnunen K, Ylä-Herttuala S. Vascular endothelial growth factors in retinal and choroidal neovascular diseases. *Ann Med*. 2012;44(1):1-17.
5. Horsley MB, Kahook MY. Anti-VEGF therapy for glaucoma. *Curr Opin Ophthalmol*. 2010;21(2):112-117.
6. Eylea® HD intravitreal injection [prescribing information]. Tarrytown, NY: Regeneron; August 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/16/2022
Selected Revision	**Retinopathy of Prematurity:** This condition was moved to the FDA-Approved Indications; previously, it was included in the Note of examples of Other Neovascular Diseases of the Eye, under "Other Uses with Supportive Evidence". For this indication, the dosing was changed to be 0.4 mg administered per injection, with the dosing interval changed to be not more frequent than once every 10 days for each eye being treated (previously, it was the same as Other Neovascular Diseases of the Eye, which was 2 mg per treated eye, with a dosing interval of at least 25 days between doses).	02/22/2023
Selected Revision	**Eylea HD:** Eylea HD was added to the policy; conditions and criteria for approval were added to the policy.	08/30/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Ranibizumab Products Utilization Management Medical Policy
- Byooviz™ (ranibizumab-nuna intravitreal injection – Biogen)
- Cimerli™ (ranibizumab-eqrn intravitreal injection – Coherus)
- Lucentis® (ranibizumab intravitreal injection – Genentech)

REVIEW DATE: 11/16/2022

OVERVIEW

Lucentis and Cimerli (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 (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**.

The recommended dose for Lucentis and Cimerli in diabetic macular edema and diabetic retinopathy is 0.3 mg administered by intravitreal injection once every month (approximately 28 days). The recommended dose for Byooviz, Cimerli, and Lucentis in neovascular (wet) age-related macular degeneration, macular edema following retinal vein occlusion, and myopic choroidal neovascularization is 0.5 mg administered by intravitreal injection once every month (approximately 28 days).

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 also have the potential to be used off-label and reduce vision loss associated with other eye conditions related to increased VEGF production. 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.[4,5] Anti-VEGF therapy has the potential to be used off-label in other neovascular conditions affecting the eye and may prevent or slow visual impairment.[2,4,5]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of ranibizumab products. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e.,

Medical Director or Pharmacist). 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

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1. Diabetic Macular Edema. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both criteria (A and B):
A) The dose is 0.3 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

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2. Diabetic Retinopathy. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both criteria (A and B):
A) The dose is 0.3 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

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3. Macular Edema Following Retinal Vein Occlusion. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both criteria (A and B):
A) The dose is 0.5 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

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4. Myopic Choroidal Neovascularization. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both criteria (A and B):
A) The dose is 0.5 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

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5. Neovascular (Wet) Age-Related Macular Degeneration. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the dose meets both criteria (A and B):
A) The dose is 0.5 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

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.

Dosing. Approve if the dose meets both criteria (A and B):
A) The dose is 0.5 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 25 days for each eye being treated.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of ranibizumab 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

1. Lucentis® intravitreal injection [prescribing information]. South San Francisco, CA: Genentech; October 2020.
2. Barakat MR, Kaiser PK. VEGF inhibitors for the treatment of neovascular age-related macular degeneration. *Expert Opin Investig Drugs*. 2009;18(5):637-646.
3. Tolentino M. Systemic and ocular safety of intravitreal anti-VEGF therapies for ocular neovascular disease. *Surv Ophthalmol*. 2011;56(2):95-113.
4. Kinnunen K, Ylä-Herttuala S. Vascular endothelial growth factors in retinal and choroidal neovascular diseases. *Ann Med*. 2012;44(1):1-17.
5. Horsley MB, Kahook MY. Anti-VEGF therapy for glaucoma. *Curr Opin Ophthalmol*. 2010;21(2):112-117.
6. Byooviz™ intravitreal injection [prescribing information]. Cambridge, MA: Biogen; September 2022.
7. Cimerli™ intravitreal injection [prescribing information]. Redwood City, CA: Coherus; October 2022.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Macular Edema Following Retinal Vein Occlusion, Myopic Choroidal Neovascularization,** and **Neovascular (Wet) Age-Related Macular Degeneration:** To align with the FDA-approved dosing, the dose was changed from "≤ 0.5 mg" to "is 0.5 mg". **Diabetic Macular Edema** and **Diabetic Retinopathy:** To align with the FDA-approved dosing, the dose was changed from "≤ 0.3 mg" to "is 0.3 mg". **Other Neovascular Ophthalmic Conditions:** Examples of other neovascular diseases of the eye were moved to a Note. To align with the FDA-approved dosing, the dose was changed from "≤ 0.5 mg" to "is 0.5 mg".	11/10/2021
Selected Revision	**Title:** The name was changed by replacing "Lucentis" with "Ranibizumab Products". Now reads, Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Ranibizumab Products Utilization Management Medical Policy. **Product:** Byooviz was added to the same conditions for approval as for Lucentis.	06/08/2022
Selected Revision	**Product:** Cimerli was added to the same conditions for approval as for the other ranibizumab products.	08/10/2022
Annual Revision	No criteria changes.	11/16/2022

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Vabysmo Utilization Management Medical Policy
- Vabysmo™ (faricimab-svoa intravitreal injection – Genentech/Roche)

REVIEW DATE: 11/16/2022

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).
- **Neovascular (wet) age-related macular degeneration** (nAMD).

Dosing Information

The recommended initial dose for nAMD and DME is 6 mg administered by intravitreal injection once every 4 weeks.[1] Dosing frequency is based on clinical evaluation and may be modified by extensions of up to 4 week interval increments or reductions of up to 8 week interval increments.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Vabysmo. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. 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

1. Diabetic Macular Edema. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the requested dosing meets the following (A and B):
A) The dose is 6 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 4 weeks for each eye being treated.

2. Neovascular (Wet) Age-Related Macular Degeneration. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Dosing. Approve if the requested dosing meets the following (A and B):
A) The dose is 6 mg administered by intravitreal injection for each eye being treated; AND
B) The dosing interval is not more frequent than once every 4 weeks for each eye being treated.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vabysmo 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. Vabysmo™ intravitreal injection [prescribing information]. South San Francisco, CA: Genentech/Roche; January 2022.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	02/09/2022
Early Annual Revision	**Neovascular (Wet) Age-Related Macular Degeneration:** The dosing interval was changed to not more frequent than once every 4 weeks.	11/16/2022

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Pompe Disease – Enzyme Replacement Therapy – Lumizyme Utilization Management Medical 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 medical benefit coverage of Lumizyme. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **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.

   Dosing. Each dose must not exceed 20 mg/kg administered intravenously no more frequently than once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lumizyme 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. Lumizyme® intravenous infusion [prescribing information]. Cambridge, MA: Genzyme; July 2021.
2. Chien YH, Hwu WL, Lee NC. Pompe disease: Early diagnosis and early treatment make a difference. *Pediatr Neonatol*. 2013;54:219-227.
3. 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.
4. Cupler EJ, Berger KI, Leshner RT, et al. Consensus treatment recommendations for late-onset Pompe disease. *Muscle Nerve*. 2012;45:319-333.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/06/2022
Annual Revision	No criteria changes.	04/12/2023
Update	10/04/2023: No criteria changes. Policy name changed from Enzyme Replacement Therapy – Lumizyme to Pompe Disease – Enzyme Replacement Therapy – Lumizyme.	NA

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Pompe Disease – Enzyme Replacement Therapy – Nexviazyme Utilization Management Medical 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 medical benefit coverage of Nexviazyme. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

1. **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.

Dosing. Approve one of the following dosing regimens (A or B):
A) Patient ≥ 30 kg: Dose is 20 mg/kg administered by intravenous infusion once every 2 weeks; OR
B) Patient < 30 kg: Dose is 40 mg/kg administered by intravenous infusion once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nexviazyme 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. Nexviazyme ® intravenous infusion [prescribing information]. Cambridge, MA: Genzyme; April 2023.
2. Chien YH, Hwu WL, Lee NC. Pompe disease: Early diagnosis and early treatment make a difference. *Pediatr Neonatol*. 2013;54:219-227.
3. 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.
4. Cupler EJ, Berger KI, Leshner RT, et al. Consensus treatment recommendations for late-onset Pompe disease. *Muscle Nerve*. 2012;45:319-333.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/10/2022
Annual Revision	No criteria changes.	08/23/2023
Update	10/04/2023: No criteria changes. Policy name changed from Enzyme Replacement Therapy – Nexviazyme to Pompe Disease – Enzyme Replacement Therapy – Nexviazyme.	NA

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Proprotein Convertase Subtilisin Kexin Type 9 Related Products – Leqvio Utilization Management Medical 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 medical benefit coverage of Leqvio. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Leqvio as well as the monitoring required for adverse events and long-term efficacy, 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

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1. 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

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.

Dosing. Approve ONE of the following dosage regimens (A or B):

A) Initial dose is 284 mg given as a single subcutaneous injection, again at 3 months, and then once every 6 months; OR

B) Maintenance dose is 284 mg given as a subcutaneous injection once every 6 months.

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2. 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.

Dosing. Approve ONE of the following dosage regimens (A or B):

A) Initial dose is 284 mg given as a single subcutaneous injection, again at 3 months, and then once every 6 months; OR

B) Maintenance dose is 284 mg given as a subcutaneous injection once every 6 months.

Other Uses with Supportive Evidence

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3. 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, 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 history 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

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.

Dosing. Approve ONE of the following dosage regimens (A or B):

A) Initial dose is 284 mg given as a single subcutaneous injection, again at 3 months, and then once every 6 months; OR

B) Maintenance dose is 284 mg given as a subcutaneous injection once every 6 months.

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:

1. **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.

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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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/03/2022
Early Annual Revision	No criteria changes. The header of the policy was changed from "Hyperlipidemia" to "Proprotein Convertase Subtilisin Kexin Type 9 Related Products."	04/13/2022
Annual Revision	It was added to the Policy Statement that 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 Levqio, initial criteria must be met. In addition, the following changes were made: **Atherosclerotic Cardiovascular Disease:** Requirements were divided to distinguish between initial therapy and patient currently receiving Leqvio (previously there was only one criteria set). For a patient who is currently receiving Leqvio and has previously met initial therapy criteria for the requested indication under the Coverage Review Department, only the continuation of therapy criteria has to be met. The continuation of therapy criteria states that according to the prescribing physician, the patient has experienced a response to therapy with examples provided in a Note. **Heterozygous Familial Hypercholesterolemia:** Requirements were divided to distinguish between initial therapy and patient currently receiving Leqvio (previously there was only one criteria set). The criteria to confirm the diagnosis of heterozygous familial hypercholesterolemia were reworded regarding the use of the Dutch Lipid Network criteria and the Simon Broome criteria; also, the phrase "prescriber used" was changed to "the prescribing physician confirms". For a patient who is currently receiving Leqvio and has previously met initial therapy criteria for the requested indication under the Coverage Review Department, only the continuation of therapy criteria has to be met. The continuation of therapy criteria states that according to the prescribing physician, the patient has experienced a response to therapy with examples provided in a Note.	04/26/2023
Selected Revision	**Atherosclerotic Cardiovascular Disease:** The condition was moved from FDA-Approved Indications to Other Uses with Supportive Evidence. Also, coronary artery disease was added as a condition or diagnosis that represents this indication of use in this related requirement. A Note was added that a patient may have a diagnoses that pertains to more than one indication, therefore, consider review under different approval conditions, if applicable. **Heterozygous Familial Hypercholesterolemia:** A Note was added that a patient may have a diagnoses that pertains to more than one indication, therefore, consider review under different approval conditions, if applicable. **Primary Hyperlipidemia:** This was added as a new FDA-approved indication.	08/30/2023

APPENDIX A

Simon Broome Register Diagnostic Criteria.[9]

Definite Familial Hypercholesterolemia
Raised cholesterol
--Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a patient < 16 years of age; OR
--Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in a patient > 16 years of age;
AND
--Tendon xanthomas in the patient or in a first (parent, sibling, or child) or second-degree relative (grandparent, aunt, or uncle);
OR
DNA-based evidence of LDL-receptor, familial defective APOB, or PCSK9 mutation.
Possible (or Probable) Familial Hypercholesterolemia
Raised cholesterol
--Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a patient < 16 years of age; OR
--Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in a patient > 16 years of age;
AND
Family history of premature myocardial infarction younger than 50 years of age in second-degree relative or younger than 60 years of age in first-degree relative;
OR
Raised cholesterol
--Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a patient < 16 years of age; OR
--Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in a patient > 16 years of age;
AND
Family history of raised cholesterol > 7.5 mmol (290 mg/dL) in adult first-degree or second-degree relative or > 6.7 mmol/L (260 mg/dL) in child or sibling aged < 16 years.

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]

Criteria	Score
Family History	
First-degree relative with known premature coronary and/or vascular disease (men < 55 years, women < 60 years)	1
First degree relative with known LDL-C > 95th percentile for age and sex	1
First-degree relative with tendon xanthomata and/or arcus cornealis, OR	2
Patient is < 18 years of age with LDL-C > 95th percentile for age and sex	2
Clinical History	
Patient with premature CAD (age as above)	2
Patient with premature cerebral or peripheral vascular disease (age as above)	1
Physical Examination	
Tendon xanthomas	6
Arcus cornealis at age < 45 years	4
LDL-C	
LDL-C ≥ 8.5 mmol/L (330 mg/dL)	8
LDL-C 6.5 to 8.4 mmol/L (250 to 329 mg/dL)	5
LDL-C 5.0 to 6.4 mmol/L (190 to 249 mg/dL)	3
LDL-C 4.0 to 4.9 mg/dL (155 to 189 mg/dL)	1
DNA Analysis	
Functional mutation LDLR, APOB or PCSK9 gene	8
Stratification	**Total score**
Definite familial hypercholesterolemia	> 8
Probable familial hypercholesterolemia	6 to 8
Possible familial hypercholesterolemia	3 to 5
Unlikely familial hypercholesterolemia	< 3

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.

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Psychiatry – Spravato Utilization Management Medical Policy
- Spravato® (esketamine nasal spray – Janssen)

REVIEW DATE: 05/31/2023

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 medical benefit coverage of Spravato. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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1. **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.

   Dosing. Approve the following dosing regimen (A and B):
   - **A)** Maximum single dose: 84 mg intranasally; AND
   - **B)** Twice weekly dosing for 4 weeks.

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2. **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; 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 history 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.

Dosing. Approve the following dosing regimen (A, B, and C):

A) Maximum single dose: 84 mg intranasally; AND

B) Induction phase (Weeks 1 to 4): twice weekly dosing; AND

C) Maintenance phase (Weeks 5 and after): up to once weekly dosing.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Spravato 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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/20/2022
Annual Revision	**Treatment-Resistant Depression:** Removed "unless unavailable in the state" from criterion requiring the "patient's history of controlled substance prescriptions has been checked using the state prescription drug monitoring program (PDMP)." Removed Note regarding Missouri not having a statewide PDMP (legislation was enacted in 2021). **Policy Statement:** A Note was added to the Policy Statement to clarify that 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. Additionally, 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.	05/31/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Psychiatry – Zulresso Utilization Management Medical 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.

Dosing Information
Zulresso is administered as a continuous intravenous infusion over 60 hours.[1] If excessive sedation occurs during the infusion, the infusion should be stopped until the symptoms resolve, then the infusion may be restarted at the same or a lower dose as clinically appropriate. The dose titration schedule for Zulresso is provided in Table 1.

Table 1. Dose Titration Schedule of Zulresso.[1]

Time	Infusion rate
0 to 4 hours	30 mcg/kg/hour
4 to 24 hours	60 mcg/kg/hour
24 to 52 hours	90 mcg/kg/hour (a reduction in dose to 60 mcg/kg/hour may be considered during this time period for patients who do not tolerate 90 mcg/kg/hour)
52 to 56 hours	60 mcg/kg/hour
56 to 60 hours	30 mcg/kg/hour

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 medical benefit coverage of Zulresso. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. 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 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.
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

1. **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.

   Dosing. Approve up to 90 mcg/kg/hour given intravenously as a one-time, 60-hour infusion once per postpartum period.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zulresso is not recommended in the following situations:

1. **Previous Treatment with Zulresso during the Current Episode of Postpartum Depression**.

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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	05/25/2022
Selected Revision	**Postpartum Depression:** Change in age criterion from ≥ 18 years of age to ≥ 15 years of age.	07/13/2022
Annual Revision	No criteria changes.	06/07/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Pulmonary Arterial Hypertension – Epoprostenol Products Utilization Management Medical Policy

- Flolan® (epoprostenol intravenous infusion – GlaxoSmithKline, generic)
- Veletri® (epoprostenol intravenous infusion – Actelion)

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 intravenous infusion 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 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.[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 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. 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 medical benefit coverage of epoprostenol. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 Utilization Management Medical 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 Utilization Management Medical 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

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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 [(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), 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 meets 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 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 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 and b):
       - **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.

Dosing. Approve up to 100 ng/kg/minute intravenously.

Other Uses with Supportive Evidence

2. Chronic Thromboembolic Pulmonary Hypertension (CTEPH). Approve for 1 year if the agent is prescribed by or in consultation with a pulmonologist or a cardiologist.

Dosing. Approve up to 45 ng/kg/minute intravenously.

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 injection (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.

REFERENCES

1. Flolan® intravenous infusion [prescribing information]: Research Triangle Park: NC; GlaxoSmithKline; August 2021.
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10. Papamatheakis DG, Poch DS, Fernandes TM, et al. Chronic thromboembolic pulmonary hypertension: JACC focus seminar. *J Am Coll Cardiol*. 2020;76(180):2155-2169.
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13. Maron B. Revised definition of pulmonary hypertension and approach to management: a clinical primer. *J Am Heart Assoc*. 2023 April 7. [epub ahead of print].

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Pulmonary Arterial Hypertension (World Health Organization Group 1):** Tyvaso DPI was added as an example of a prostacyclin product used for pulmonary arterial hypertension. Tadliq was added as an example of an oral agent used for pulmonary arterial hypertension. **Conditions Not Recommended for Approval:** It was added that concurrent use with parenteral treprostinil products, oral prostacyclin products, or inhaled prostacyclin agents used for pulmonary hypertension is not permitted. Examples of medications were provided in a Note.	10/05/2022
Annual Revision	No criteria changes.	10/04/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Pulmonary Arterial Hypertension – Treprostinil Injection Utilization Management Medical 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 medical benefit coverage of treprostinil injection. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 Utilization Management Medical 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 Utilization Management Medical 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

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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 criteria (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, 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
           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 [(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 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 patients 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 Treprostinil Injection. 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 both of 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 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.

Dosing. Approve up to 100 ng/kg/minute given subcutaneously or intravenously.

Other Uses with Supportive Evidence

2. Chronic Thromboembolic Pulmonary Hypertension (CTEPH). Approve for 1 year if the agent is prescribed by or in consultation with a pulmonologist or a cardiologist.

Dosing. Approve up to 50 ng/kg/minute subcutaneously or intravenously.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of treprostinil 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 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).

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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	The word "Remodulin" was removed from the name of the policy. In addition, the following changes were made. **Pulmonary Arterial Hypertension (World Health Organization Group 1):** Tyvaso DPI was added as an example of a prostacyclin product used for pulmonary arterial hypertension. Tadliq was added as an example of an oral agent used for pulmonary arterial hypertension. **Conditions Not Recommended for Approval:** It was added that concurrent use with with parenteral epoprostenol products, oral prostacyclin products, or inhaled prostacyclin agents used for pulmonary hypertension is not permitted. Examples of medications are provided in a Note.	10/05/2022
Annual Revision	No criteria changes.	10/04/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Scenesse Utilization Management Medical 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 medical benefit coverage of Scenesse. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the dosing interval is provided in months, 1 month is equal to 30 days. 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

1. **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 history 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.

   Dosing. Approve a single Scenesse implant (containing 16 mg of afamelanotide) to be inserted subcutaneously no more frequently than once every 2 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Scenesse 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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	02/23/2022
Early Annual Revision	No criteria changes.	01/11/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Somatostatin Analogs – Sandostatin LAR Depot Utilization Management Medical 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 medical coverage of Sandostatin LAR Depot. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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.

*Indications and/or approval conditions noted with **[eviCore]** are managed by eviCore healthcare for those clients who use eviCore for oncology and/or oncology-related reviews. For these conditions, a prior authorization review should be directed to eviCore at www.eviCore.com.*

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sandostatin LAR Depot is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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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 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.

C) The medication is prescribed by or in consultation with an endocrinologist.

Dosing. Approve up to 40 mg administered intramuscularly no more frequently than once every 4 weeks.

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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). ***[eviCore]*** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist, endocrinologist, or gastroenterologist.

Dosing. Approve up to 30 mg administered intramuscularly no more frequently than once every 4 weeks.

Other Uses with Supportive Evidence

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3. Meningioma. ***[eviCore]*** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist, radiologist, or neurosurgeon.

Dosing. Approve up to 40 mg administered intramuscularly no more frequently than once every 4 weeks.

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4. **Pheochromocytoma and Paraganglioma.** ***[eviCore]*** Approve for 1 year if the medication is prescribed by or in consultation with an endocrinologist, oncologist, or neurologist.

   Dosing. Approve up to 40 mg administered intramuscularly no more frequently than once every 4 weeks.

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5. **Thymoma and Thymic Carcinoma.** ***[eviCore]*** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

   Dosing. Approve up to 40 mg administered intramuscularly no more frequently than once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sandostatin LAR Depot 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. Sandostatin® LAR Depot intramuscular injection [prescribing information]. East Hanover, NJ: Novartis; July 2023.
2. 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.
3. 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.
4. 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.
5. 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/10/2022
Annual Revision	No criteria changes.	07/28/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Spinal Muscular Atrophy – Gene Therapy – Zolgensma Utilization Management Medical 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]

SMA Type	Age at Onset	Features/Clinical Presentation	Lifespan	SMN2 Gene Copy Number
0	Prenatal	Severe hypotonia and weakness; respiratory failure at birth. There is no achievement of motor milestones.	A few weeks to < 6 months	0 to 1
1	< 6 months	Poor muscle tone, lack of movement, and respiratory assistance needed at birth. Patients are never able to sit.	< 2 years	1 to 2

Table 1 (continued). Types of Spinal Muscular Atrophy.[3-6]

SMA Type	Age at Onset	Features/Clinical Presentation	Lifespan	SMN2 Gene Copy Number
2	Before 18 months	Patients are able to sit. However, patients are unable to walk or stand without assistance.	75% of patients are alive at 25 years of age	2 to 3
3	> 18 months	Walks independently but may lose this ability as the disease progresses.	Normal	3 to 4
4	Adulthood	Walk until adulthood.	Normal	≥ 4

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** and **Dosing** 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

1. **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):
   - **A)** Patient is less than 2 years of age; AND
   - **B)** 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.
   - **C)** 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.
   - **D)** Patient meets one of the following (i or ii):
     - **i.** Patient has three or fewer survival motor neuron 2 (SMN2) gene copies **[documentation required]**; OR
     - **ii.** Patient meets both of the following (a and b):
       - **a)** Patient has four survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND
       - **b)** 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
   - **E)** 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 and for a total of 30 days; AND
   - **F)** Baseline anti-AAV9 antibody titers are ≤ 1:50 **[documentation required]**; AND
   - **G)** Patient has undergone a liver function assessment within the last 30 days and meets all of the following (i, ii, iii, and iv):
     - **i.** Alanine aminotransferase levels are ≤ 2 times the upper limit of normal **[documentation required]**; AND
     - **ii.** Aspartate aminotransferase levels are ≤ 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
       Note: Patient with elevated bilirubin levels due to neonatal jaundice are acceptable.
     - **iv.** Prothrombin time results are ≤ 2 times the upper limit of normal **[documentation required]**; AND
   - **H)** Patient has undergone a renal function assessment within the last 30 days and has a creatinine level < 1.0 mg/dL **[documentation required]**; AND

I) A complete blood count has been obtained within the last 30 days and the patient meets both of the following (i and ii):
  i. White blood cell count is ≤ 20,000 cells per mm^3 **[documentation required]**; AND
  ii. Hemoglobin levels are between 8 g/dL and 18 g/dL **[documentation required]**; AND

J) Patient has not received Zolgensma 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.

K) 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

L) 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

M) 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

N) If criteria A through M are met, approve one single intravenous infusion of Zolgensma at a dose of 1.1×10^{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.

Dosing. The recommended dose of Zolgensma for single-dose intravenous infusion is 1.1×10^{14} vector genomes (vg)/kg based on the current patient weight in kg (within the last 14 days). Zolgensma is provided as a customized kit to meet dosing requirements for each patient per their documented weight (in kilograms). Refer to the appropriate NDC number below for approval.

Table 2. Dose of Zolgensma Based on Availability.[1]

Patient Weight Range (kg)	Dose Volume (mL)*	Zolgensma Kit Configuration			NDC Number
		5.5 mL vial	8.3 mL vial	Total Vials per Kit	
2.6 to 3.0	16.5	0	2	2	71894-120-02
3.1 to 3.5	19.3	2	1	3	71894-121-03
3.6 to 4.0	22.0	1	2	3	71894-122-03
4.1 to 4.5	24.8	0	3	3	71894-123-03
4.6 to 5.0	27.5	2	2	4	71894-124-04
5.1. to 5.5	30.3	1	3	4	71894-125-04
5.6 to 6.0	33.0	0	4	4	71894-126-04
6.1 to 6.5	35.8	2	3	5	71894-127-05
6.6 to 7.0	38.5	1	4	5	71894-128-05
7.1 to 7.5	41.3	0	5	5	71894-129-05
7.6 to 8.0	44.0	2	4	6	71894-130-06
8.1 to 8.5	46.8	1	5	6	71894-131-06
8.6 to 9.0	49.5	0	6	6	71894-132-06
9.1 to 9.5	52.3	2	5	7	71894-133-07
9.6 to 10.0	55.0	1	6	7	71894-134-07
10.1 to 10.5	57.8	0	7	7	71894-135-07
10.6 to 11.0	60.5	2	6	8	71894-136-08
11.1 to 11.5	63.3	1	7	8	71894-137-08
11.6 to 12.0	66.0	0	8	8	71894-138-08
12.1 to 12.5	68.8	2	7	9	71894-139-09
12.6 to 13.0	71.5	1	8	9	71894-140-09
13.1 to 13.5	74.3	0	9	9	71894-141-09
13.6 to 14.0	77.0	2	8	10	71894-142-10
14.1 to 14.5	79.8	1	9	10	71894-143-10
14.6 to 15.0	82.5	0	10	10	71894-144-10
15.1 to 15.5	85.3	2	9	11	71894-145-11
15.6 to 16.0	88.0	1	10	11	71894-146-11
16.1 to 16.5	90.8	0	11	11	71894-147-11
16.6 to 17.0	93.5	2	10	12	71894-148-12
17.1 to 17.5	96.3	1	11	12	71894-149-12
17.6 to 18.0	99.0	0	12	12	71894-150-12
18.1 to 18.5	101.8	2	11	13	71894-151-13
18.6 to 19.0	104.5	1	12	13	71894-152-13
19.1 to 19.5	107.3	0	13	13	71894-153-13
19.6 to 20.0	110.0	2	12	14	71894-154-14
20.1 to 20.5	112.8	1	13	14	71894-155-14
20.6 to 21.0	115.5	0	14	14	71894-156-14

* Dose volume is calculated using the upper limit of the patient weight range for pediatric patients < 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:

1. **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 with advanced spinal muscular atrophy would derive benefits from Zolgensma.

2. **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 with advanced spinal muscular atrophy would derive benefits from Zolgensma.

3. **Administration to Individuals In Utero.** Zolgensma is not approved for in utero administration per the prescribing information.

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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	10/05/2022
Selected Revision	The terminology, "Gene Therapy" was added to the title of the policy. For operational reasons, it was added to the Policy Statement that the approval duration is 1 month to allow for an adequate timeframe to prepare and administer one dose of therapy. In addition, the following changes were made: **Spinal Muscular Atrophy – Treatment:** Previously, a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 gene reported as at least one of the following was required: homozygous deletion, homozygous mutation, or compound heterozygous mutation [documentation required]. This was revised to state that a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic pathogenic variants in the survival motor neuron 1 gene [documentation required] is required with a Note added stating that pathogenic variants may include homozygous deletion, compound heterozygous mutation, or a variety of other rare mutations. Regarding the requirement that the patient has started or will receive systemic corticosteroids, the wording "According to the prescribing physician" was added. A documentation requirement was added to the requirement that baseline anti-AAV9 antibody titers are ≤ 1:50. Previously, baseline liver function testing was required before Zolgensma administration, with a Note stating that examples of tests include aspartate aminotransferase, alanine aminotransferase, total bilirubin, and prothrombin time. The requirement was revised to state that the patient has undergone a liver function assessment within the last 30 days and meets all of the following criteria: alanine aminotransferase levels are ≤ 2 times the upper limit of normal [documentation required]; aspartate aminotransferase levels are ≤ 2 times the upper limit of normal [documentation required]; total bilirubin levels are ≤ 2 times the upper limit of normal [documentation required] {with a Note stating that elevated bilirubin levels due to neonatal jaundice are acceptable}; and prothrombin time results are ≤ 2 times the upper limit of normal [documentation required]. Previously, creatinine was required to be examined prior to administration of Zolgensma; this was revised to state that the patient was undergone a renal function assessment within the last 30 days and has a creatinine level < 1.0 mg/dL [documentation required]. Previously, a complete blood count was required to be examined prior to administration (including hemoglobin and platelet counts). This requirement was revised to state a complete blood count has been obtained within the last 30 days and the patient has a white blood cell count ≤ 20,000 cells per mm^3 [documentation required] and hemoglobin levels are between 8 g/dL and 18 g/dL [documentation required]. The requirement to examine troponin I levels prior to administration of Zolgensma was deleted. The criteria that state "prescriber" were changed to "prescribing physician". **Dosing:** The Dosing section was revised (refer to the policy) and 15 additional NDC numbers were added to reflect Zolgensma kit configurations available in weights ranging from 13.6 to 21.0 kg. **Conditions Not Recommended for Approval:** Administration to Individuals in Utero was added as a new situation in which use of Zolgensma is not approved.	3/22/2023
Annual Revision	For Spinal Muscular Atrophy, regarding the requirement which mandates that a premature neonate to reach full term gestational age of 39 weeks and 0 days, a Note was added that full-term gestational age can be defined as the postmenstrual age (gestational age plus chronological age) being equal to ≥ 39 weeks and 0 days.	11/01/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Spinal Muscular Atrophy – Spinraza Utilization Management Medical 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 Type	Age at Onset	Features/Clinical Presentation	Lifespan	SMN2 Copy Gene Number
0	Prenatal	Severe hypotonia and weakness; respiratory failure at birth. There is no achievement of motor milestones.	A few weeks to < 6 months	0 to 1
1	< 6 months	Poor muscle tone, lack of movement, and respiratory assistance needed at birth. Patients are never able to sit.	< 2 years	1 to 2
2	Before 18 months	Patients are able to sit. However, patients are unable to walk or stand without assistance.	75% of patients are alive at 25 years of age	2 to 3
3	> 18 months	Walks independently but may lose this ability as the disease progresses.	Normal	3 to 4
4	Adulthood	Walk until adulthood.	Normal	≥ 4

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 medical benefit coverage of Spinraza. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 Utilization Management Medical 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

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1. 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):

i. Baseline motor ability assessment that suggest 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

Note: Pathogenic variants may include homozygous deletion, compound heterozygous mutation, or a variety of other rare mutations.

iii. 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

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 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. 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 (one 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)]:
  - **(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. 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 suspension for 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.

vi. 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

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.

Dosing. Approve the following dosing regimens:

A) Initially give 12 mg intrathecally as four loading doses of which the first three loading doses should be given at 14-day intervals and the fourth loading dose should be given 30 days after the third dose; AND/OR

B) The maintenance dose is 12 mg intrathecally once every 4 months; AND/OR

C) Missed maintenance doses must meet the following (i, ii, or iii):

i. At least 8 months but less than 16 months from the last dose: approve one 12 mg intrathecal dose to be given as soon as possible, followed by one additional dose 14 days later; OR

Note: Thereafter, the regular maintenance dose schedule should be followed.

ii. At least 16 months but less than 40 months from the last dose: approve the 12 mg intrathecal maintenance dose to be given as soon as possible, followed by two additional doses that must be given 14 days apart; OR
Note: Thereafter, the regular maintenance dose schedule should be followed.

iii. At least 40 months from the last dose. Dosing should be restarted as recommended in criterion A and B.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Spinraza is not recommended in the following situations:

1. **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.

2. **Patient has Permanent Ventilator Dependence.** Data are needed to determine if this patient population with advanced spinal muscular atrophy would derive benefits from Spinraza.

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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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	10/05/2022
Selected Revision	**Spinal Muscular Atrophy – Treatment:** For both Initial Therapy and for a Patient Currently Receiving Spinraza Therapy, the reference to the Bayley Scales of Infant and Toddler Development had the descriptor of "Third Edition (BSID-III) [Item 22]" removed; this scale is still noted in criteria as an updated edition has been released. Previously, a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 gene reported as at least one of the following was required: homozygous deletion, homozygous mutation, or compound heterozygous mutation [documentation required]. This was revised to state that a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic pathogenic variants in the survival motor neuron 1 gene [documentation required] is required with a Note added stating that pathogenic variants may include homozygous deletion, compound heterozygous mutation, or a variety of other rare mutations. The phrase "according to the prescriber" was removed from the requirement that the patient has objective signs consistent with spinal muscular atrophy Types 1, 2, and 3 since documentation is required. The criteria that state "prescriber" were changed to "prescribing physician". The requirement of the following laboratory tests to be performed prior to administration of Spinraza were deleted: prothrombin time and/or activated partial thromboplastin time, platelet count, and quantitative spot urine protein testing. The phrase "verification in claims history required" replaced the previous wording of "verification required by prescriber". **Dosing:** Recommendations were added regarding missed maintenance doses. Refer to the policy.	03/22/2023
Annual Revision	No criteria changes.	11/01/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Synagis Utilization Management Medical 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 history 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 and reaffirmed in 2023.[3,13] 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).[12] 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 medical benefit coverage of Synagis. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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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):
     - **i.** Patient was born at < 32 weeks, 0 days gestation; AND
     - **ii.** 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):
     - **i.** Patient was born at < 32 weeks, 0 days gestation; AND
     - **ii.** Patient required > 21% oxygen for at least 28 days after birth; AND
     - **iii.** 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.

   Dosing. Approve a dose of 15 mg/kg given intramuscularly once monthly during the RSV season.

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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):
       - **a)** Patient has acyanotic heart disease; AND
       - **b)** Patient is receiving medication to control heart failure; AND
       - **c)** 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):
       - **a)** Patient has lesions that have been adequately corrected by surgery; AND
       - **b)** Patient continues to require medication for congestive heart failure; AND
   - **C)** Synagis is prescribed by or in consultation with a cardiologist or intensivist.

   Dosing. Approve a dose of 15 mg/kg given intramuscularly once monthly during the RSV season.

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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).

   Dosing. Approve a dose of 15 mg/kg given intramuscularly once monthly during the RSV season.

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.

   Dosing. Approve a dose of 15 mg/kg given intramuscularly once monthly during the RSV season.

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.

   Dosing. Approve a dose of 15 mg/kg given intramuscularly once monthly during the RSV season.

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):
   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.

   Dosing. Approve a dose of 15 mg/kg given intramuscularly once monthly during the RSV season.

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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HISTORY

Type of Revision	Summary of Changes	Review Date
Update	**02/03/2022:** No criteria changes. The policy statement was updated with coverage recommendations for the 2021-2022 winter respiratory syncytial virus (RSV) season, in alignment with American Academy of Pediatrics recommendations. Approval durations will be authorized to align with usual RSV seasonality for the region, regardless of any doses received prior to the usual season during 2021 interseasonal spread. Doses received during interseasonal spread (i.e., outside of typical RSV seasonality for the region) do not count toward the maximum approvable five monthly doses for the 2021-2022 winter season.	NA
Early Annual Revision	**Policy Statement:** The policy statement was updated to remove the coverage recommendations for the 2021-2022 winter respiratory syncytial virus (RSV) season (see Update 2/03/2022 above). A new statement was added to define the RSV season: RSV season onset is defined as the first 2 consecutive weeks when the percentage of positive tests for RSV is > 3% by polymerase chain reaction (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.	08/10/2022
Annual Revision	**Conditions Not Recommended for Approval:** Use in a patient who has received Beyfortus (nirsevimab-alip intramuscular injection) in the same RSV season was added as a condition not recommended for approval.	08/16/2023
Update	**09/05/2023:** No criteria changes. Published recommendations for Beyfortus from the Advisory Committee on Immunization Practices as well as the American Academy of Pediatrics were added to the overview and supportive text.	09/05/2023
Update	**10/24/2023:** No criteria changes. Centers for Disease Control and Prevention health alert advisory information added to the overview.	10/24/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Thrombocytopenia – Nplate Utilization Management Medical 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 guidlines.

- **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 medical benefit coverage of Nplate. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing

documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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 long-term 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

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1. Hematopoietic Syndrome of Acute Radiation Syndrome. Approve for one dose if the patient has been acutely exposed to myelosuppressive doses of radiation.

Dosing. Approve up to 10 mcg/kg administered subcutaneously given once.

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2. 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)]:
    - **(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
- **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) and 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):

- **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.

Dosing. Approve up to 10 mcg/kg subcutaneously no more frequently than once weekly.

Other Uses with Supportive Evidence

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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 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.

Dosing. Approve up to 10 mcg/kg subcutaneously no more frequently than once weekly.

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4. Thrombocytopenia in Myelodysplastic Syndrome. Approve if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets all 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: An example of a response is increased platelet counts, maintenance of platelet counts, and/or decreased frequency of bleeding episodes.
- **ii.** Patient remains at risk for bleeding complications.

Dosing. Approve up to 1,500 mcg subcutaneously no more frequently than twice weekly.

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

1. Nplate® subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; February 2022.
2. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv*. 2019;3(23):3829-3866.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Immune Thrombocytopenia:** The wording of "Continuation of Therapy" was changed to "Patient is Currently Receiving Nplate." **Thrombocytopenia in Myelodysplastic Syndrome:** The wording of "Continuation of Therapy" was changed to "Patient is Currently Receiving Nplate."	03/23/2022
Annual Revision	No criteria changes.	04/12/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Transplantation – Nulojix Utilization Management Medical Policy
- Nulojix® (belatacept intravenous infusion – Bristol-Myers Squibb)

REVIEW DATE: 08/16/2023

OVERVIEW

Nulojix, a selective T-cell costimulation blocker, is indicated for **prophylaxis of organ rejection** in patients ≥ 18 years of age receiving a kidney transplant.[1] Nulojix is to be used in conjunction with basiliximab, mycophenolate mofetil, and corticosteroids.

The prescribed dose must be evenly divisible by 12.5 mg.[1] Use of higher than recommended doses or more frequent administration is not recommended due to the increased risk of post-transplant lymphoproliferative disorder predominately of the central nervous system (CNS), progressive multifocal leukoencephalopathy, and serious CNS infections. The dose is based on actual body weight of the patient at the time of transplantation and should not be modified during the course of treatment unless the patient's weight changes by > 10%.

Guidelines

Nulojix is not included in the guidelines. In 2009, the Kidney Disease Improving Global Outcomes (KDIGO) published extensive clinical practice guidelines for the care of kidney transplant recipients.[2] For maintenance therapy, it is recommended to employ a combination of immunosuppressive medications including a calcineurin inhibitor and an anti-proliferative agent, with or without corticosteroids. Compared to cyclosporine, tacrolimus reduces the risk of acute rejection and improves graft survival within the first year of transplantation. Tacrolimus is the first-line calcineurin inhibitor and it is suggested that tacrolimus (or cyclosporine) be initiated before or at the time of transplantation, rather than delayed until the onset of graft function. Mycophenolate should be used first-line as an anti-proliferative agent. Patients who are at low immunological risk and who receive induction therapy should have corticosteroid therapy discontinued during the first week post-transplantation. If a mammalian Target of Rapamycin (mTOR) inhibitor (Zortress® [everolimus], Rapamune® [sirolimus]) is used, it should not be commenced until graft function is established and surgical wounds are healed. In the case of no reported acute rejection, the lowest doses of maintenance immunosuppressive medications should be maintained 2 to 4 months post-transplant. Calcineurin inhibitors should be continued. Of note, many of the medications require the monitoring of levels (e.g., calcineurin inhibitor, mycophenolate mofetil, mTOR inhibitors).

Safety

Nulojix labeling contains a boxed warning for post-transplant lymphoproliferative disorder; other malignancies and serious infections; and use in liver transplant recipients.[1] Patients receiving Nulojix are at increased risk of developing post-transplant lymphoproliferative disorder, particularly those without immunity to the Epstein-Barr virus (EBV). Nulojix should only be used in individuals who are EBV seropositive; do not use in individuals who are EBV seronegative or with unknown EBV status. Individuals receiving Nulojix are at increased risk of developing infections or malignancies due to immunosuppression. Nulojix should not be used in liver transplant recipients due to an increased risk of graft loss and death.

Liver Transplantation

Nulojix has a boxed warning stating that use in liver transplant recipients is not recommended due to an increase risk of graft loss and death.[1]

In a partially-blinded, active-controlled, parallel group, Phase II trial (N = 260), patients receiving the first liver transplant were randomized 1:1:1:1:1 to basiliximab + Nulojix high-dose + mycophenolate mofetil; or Nulojix high-dose + mycophenolate mofetil; Nulojix low-dose + mycophenolate mofetil; tacrolimus + mycophenolate mofetil; or tacrolimus alone.[3] The primary endpoint was the composite of acute rejection, graft loss, and death at 6 months. Secondary endpoints included the incidence, severity, treatment, and outcome of acute rejection at 12 months; graft loss and death at 12 months; and change in renal function over time. At 6 months, the frequency of the composite endpoint was higher in the Nulojix groups (42% to 48%) compared to the tacrolimus groups (15% to 38%), driven mostly by a higher rate of acute rejection with Nulojix. An external Data Monitoring Committee stopped further enrollment in the Nulojix low-dose arm due to an increase in graft loss and death compared to the other arms of the study; however patients already on Nulojix low-dose were allowed to continue at the discretion of the investigator. At 12 months, there was a higher rate of acute rejection and death in the Nulojix groups compared to tacrolimus + mycophenolate mofetil. The long-term extension phase was terminated early when the Data Monitoring Committee determined there was continued graft loss and death in the Nulojix high-dose group.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Nulojix. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nulojix as well as the monitoring required for adverse events and long-term efficacy, approval requires Nulojix to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indication

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1. **Kidney Transplantation – Prophylaxis of Organ Rejection.** 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 Epstein-Barr virus (EBV) seropositive; AND
   - **C)** Nulojix is prescribed by or in consultation with a transplant specialist physician or a physician associated with a transplant center.

   Dosing. Approve the following dosing regimen (A and B):
   - **A)** Each individual dose must not exceed 10 mg/kg administered by intravenous infusion; AND
   - **B)** Nulojix is administered no more than four times in the first 4 weeks (day of transplant, Day 5, end of Week 2, and end of Week 4), and then no more frequently than once every 4 weeks.

Other Uses with Supportive Evidence

2. Solid Organ Transplantation Other Than Kidney – Prophylaxis of Solid Organ Rejection in a Patient Currently Receiving Nulojix. 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 Epstein-Barr virus (EBV) seropositive; AND
- **C)** Nulojix is prescribed by or in consultation with a transplant specialist physician or a physician associated with a transplant center.

Dosing. Approve the following dosing regimen (A and B):
- **A)** Each individual dose must not exceed 10 mg/kg administered by intravenous infusion; AND
- **B)** Nulojix is administered no more than four times in the first 4 weeks (day of transplant, Day 5, end of Week 2, and end of Week 4), and then no more frequently than once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nulojix 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. Nulojix® intravenous infusion [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; July 2021.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients. *Am J Transplant*. 2009;9(Suppl 3):S1 – S157.
3. Klintmalm GB, Feng S, Lake JR, et al. Belatacept-Based Immunosuppression in *De Novo* Liver Transplant Recipients: 1-Year Experience From a Phase II Randomized Study. *Am J Transplant*. 2014;14:1817-1827.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	07/20/2022
Annual Revision	No criteria changes.	08/16/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Transplantation – Omisirge Utilization Management Medical Policy
- Omisirge® (omidubicel-onlv intravenous infusion – Gamida)

REVIEW DATE: 08/09/2023

OVERVIEW

Omisirge, a nicotinamide modified allogeneic hematopoietic progenitor cell therapy derived from cord blood, is indicated for use in patients with hematologic malignancies who are planning to undergo umbilical cord blood transplantation following myeloablative conditioning to reduce the time to neutrophil recovery and the incidence of infection in adults and pediatric patients ≥ 12 years of age.[1]

Disease Overview

Stem cell transplantation is used to treat various hematologic malignancies and involves placing healthy stem cells into the patient to restore the normal production and function of blood cells.[2-6] Umbilical cord blood is one source of healthy stems cells used for allogeneic transplantation; others can be obtained from peripheral blood or bone marrow. After birth, the blood present in the umbilical cord and placenta contains valuable hematopoietic stems cells that are typically discarded as medical waste. However, through donation, umbilical cord blood cells can be stored and used later for patients with conditions such as hematologic malignancies. Around 70% of patients do not have an optimal matched family donor; therefore, cells can be obtained from an unrelated donor. Patients who are non-White generally have more difficulties finding a suitable donor.

Dosing Information

Omisirge is given as a single intravenous dose.[1] Omisirge is provided in two bags containing the two cryopreserved cell fractions (i.e., cultured fraction and non-cultured fraction). After it is made from the umbilical cord blood donor source, which takes about 21 days, Omisirge is shipped to the transplant center for a specific patient.

Safety

Omisirge has a Boxed Warning regarding infusion reactions, graft versus host disease, engraftment syndrome, and graft failure.[1]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Omisirge. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for one dose. The approval duration is 6 months to allow for an adequate timeframe to prepare and administer one dose of therapy.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indication

1. **Umbilical Cord Blood Transplantation.** Approve for one dose if the patient meets the following (A, B, and C):
   - **A)** Patient is ≥ 12 years of age; AND
   - **B)** Patient has a hematologic malignancy; AND
     Note: Examples of hematologic malignancies are acute myelogenous leukemia, acute lymphoblastic leukemia, and chronic myeloid leukemia.
   - **C)** Omisirge is prescribed by or in consultation with a hematologist, oncologist, transplant specialist physician, or a physician associated with a transplant center.

   Dosing. Approve a single dose of Omisirge given by intravenous infusion.
   Note: Omisirge is provided in two separate bags containing the two cryopreserved cell fractions (i.e., cultured fraction and non-cultured fraction).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Omisirge 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. Omisirge® intravenous infusion [prescribing information]. Boston, MA: Gamida; April 2023.
1. Food and Drug Administration News Release. FDA approves cell therapy for patients with blood cancers to reduce risk of infection following stem cell transplantation. April 17, 2023. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-cell-therapy-patients-blood-cancers-reduce-risk-infection-following-stem-cell. Accessed on July 19, 2023.
2. The NCCN Hematopoietic Cell Transplantation (HCT) Guidelines in Oncology (version 1.2023 – March 31, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 19, 2023.
3. Bazinet A, Popradi G. A general practitioner's guide to hematopoietic stem-cell transplantation. *Curr Oncol*. 2019;26(3):187-191.
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5. Be The Match Registry® website. "About Cord Blood" and "How does a patient's ethnic background affect matching?" Available at: https://bethematch.org/support-the-cause/donate-cord-blood/about-cord-blood/ and https://bethematch.org/transplant-basics/how-blood-stem-cell-transplants-work/how-does-a-patients-ethnic-background-affect-matching/#:~:text=This%20is%20because%20HLA%20markers,can%20make%20all%20the%20difference. Accessed on July 19, 2023.
6. Dehn J, Spellman S, Hurley CK, et al. Selection of unrelated donors and cord blood units for hematopoietic cell transplantation: guidelines from the NMDP/CIBMTR. *Blood*. 2019;134(12):924-934.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/09/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Uplizna Utilization Management Medical 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] The recommended dose is 300 mg administered as an intravenous (IV) infusion under the close supervision of an experienced healthcare professional. The initial infusion is followed 2 weeks later by a second 300 mg IV infusion. Subsequent doses are administered once every 6 months (starting 6 months after the first infusion).

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 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 medical benefit coverage of Uplizna. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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

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1. **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 history 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.

   Dosing. Approve the following dosing regimens (A or B):
   - **A)** 300 mg by intravenous infusion once every 2 weeks for two doses; OR
   - **B)** 300 mg by intravenous infusion once every 6 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Uplizna is not recommended in the following situations:

1. **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.

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. Uplizna® intravenous infusion [prescribing information]. Deerfield, IL: Horizon Therapeutics; July 2021.
2. 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.
3. Chan KH, Lee CY. Treatment of neuromyelitis optica spectrum disorders. *Int J Mol Sci*. 2021;22(16):8638.
4. Enspryng® subcutaneous injection [prescribing information]. South San Francisco, CA: Genentech; March 2022.
5. Soliris® intravenous infusion [prescribing information]. Boston, MA: Alexion; November 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	07/06/2022
Annual Revision	No criteria changes.	07/12/2023

CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Xiaflex Utilization Management Medical 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 medical benefit coverage of Xiaflex. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e.,

Medical Director or Pharmacist). 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.

Medical 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

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1. 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.

Dosing. Approve if the dose meets all of the following (A, B, and C):

- **A)** The dose is 0.58 mg per injection into an affected cord; AND
- **B)** A maximum of two cords (up to 1.16 mg) are injected per treatment visit; AND
  Note: If there are other affected cords in the same hand, treatment may be administered to those on a different day.
- **C)** For each affected cord, subsequent doses are administered no sooner than 4 weeks following the previous Xiaflex injection.

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2. 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.

Dosing. Approve if the dose meets all of the following (A and B):

- **A)** Up to a total of eight 0.58 mg injections; AND

Note: This is enough Xiaflex to treat with four dosing cycles, each consisting of two 0.58 mg injections given 1 to 3 days apart.
Note: For a patient who has already received one or more injections of Xiaflex, approve the duration requested up to the amount needed to complete one course of therapy (e.g., a patient who has received 3 injections may be approved for 5 additional injections to complete one course of therapy).

B) Cycles are separated by at least 6 weeks from the previous Xiaflex cycle.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xiaflex is not recommended in the following situations:

1. **Cosmetic Uses (e.g., cellulite of buttocks).** Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical medical benefit.

2. **Retreatment for Peyronie's Disease.** For Peyronie's disease, the safety of more than one treatment course (8 injections) is not known.[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.

REFERENCES

1. Xiaflex® intralesional injection [prescribing information]. Malvern, PA: Endo Pharmaceuticals; August 2022.
2. Brazzelli M, Cruickshank M, Tassie E, et al. Collagenase clostridium histolyticum for the treatment of Dupuytren's contracture: systematic review and economic evaluation. Southampton (UK): NIHR Journals Library; 2015 Oct. Available at: https://www.ncbi.nlm.nih.gov/books/NBK326596/. Accessed on August 31, 2023.
3. Nehra A, Alterowitz R, Culkin D, et al. Peyronie's disease: AUA guideline. *J Urol.* 2015;194(3):745-753.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	No criteria changes.	01/11/2023
Early Annual Revision	**Dupuytren's Contracture**: The verbiage for the requirement "Patient will not be treated with more than a total of three injections (maximum) per affected cord" was updated to: "As part of the current treatment course, the patient will be treated with up to three injections (maximum) per affected cord." **Conditions Not Recommended for Approval**: The condition of **Retreatment** was changed to **Retreatment for Peyronie's Disease**. For this condition, the statement was removed that "For Dupuytren's contracture, injections and finger extension procedures may be administered up to three times per cord. However, this does not limit treatment of additional cords."	09/06/2023